US009439942B2

(12) **United States Patent**
Peled et al.

(10) **Patent No.: US 9,439,942 B2**
(45) **Date of Patent: Sep. 13, 2016**

(54) **PEPTIDES AND USE THEREOF IN THE TREATMENT OF LARGE CELL LUNG CANCER**

(71) Applicant: **Biokine Therapeutics Ltd.**, Nes Ziona (IL)

(72) Inventors: **Amnon Peled**, Tel-Aviv (IL); **Ori Wald**, Tel-Aviv (IL)

(73) Assignee: **Biokine Therapeutics Ltd.**, Nes Ziona (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/395,842**

(22) PCT Filed: **Apr. 24, 2013**

(86) PCT No.: **PCT/IL2013/050352**

§ 371 (c)(1),
(2) Date: **Oct. 21, 2014**

(87) PCT Pub. No.: **WO2013/160895**

PCT Pub. Date: **Oct. 31, 2013**

(65) **Prior Publication Data**

US 2015/0125549 A1 May 7, 2015

Related U.S. Application Data

(60) Provisional application No. 61/637,334, filed on Apr. 24, 2012.

(51) **Int. Cl.**

A61K 38/10	(2006.01)
A61K 31/337	(2006.01)
A61N 5/10	(2006.01)
A61K 33/24	(2006.01)
A61K 38/08	(2006.01)
A61K 31/282	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/10*** (2013.01); ***A61K 31/282*** (2013.01); ***A61K 31/337*** (2013.01); ***A61K 33/24*** (2013.01); ***A61K 38/08*** (2013.01); ***A61N 5/10*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,179,337	A	12/1979	Davis et al.
4,342,828	A	8/1982	Takaku et al.
5,206,018	A	4/1993	Sehgal et al.
5,250,732	A	10/1993	Kogan et al.
5,492,126	A	2/1996	Hennige et al.
5,595,756	A	1/1997	Bally et al.
6,128,522	A	10/2000	Acker et al.
6,365,583	B1	4/2002	MacFarland et al.
6,576,875	B1	6/2003	Kleffner et al.
6,747,036	B2	6/2004	Gourdeau et al.
6,875,738	B1	4/2005	Clark-Lewis et al.
6,946,445	B1	9/2005	Clark-Lewis et al.
7,138,488	B2	11/2006	Fujii
7,169,750	B2	1/2007	Bridger et al.
7,291,631	B2	11/2007	Bridger et al.
7,419,667	B2	9/2008	Hatake et al.
7,423,007	B2	9/2008	Fujii et al.
7,595,298	B2	9/2009	Fujii
7,630,750	B2	12/2009	Liang et al.
8,017,585	B2	9/2011	Fujii et al.
2002/0156034	A1	10/2002	Tudan et al.
2002/0159996	A1	10/2002	Hariharan et al.
2004/0116655	A1	6/2004	Fujii
2004/0197305	A1	10/2004	Garzino-Demo et al.
2004/0209921	A1	10/2004	Bridger et al.
2005/0002939	A1	1/2005	Zlotnik et al.
2005/0043367	A1	2/2005	Bridger et al.
2005/0265969	A1	12/2005	Clark-Lewis et al.
2006/0008465	A1	1/2006	Steinaa et al.
2006/0035829	A1	2/2006	Bridger et al.
2006/0079492	A1	4/2006	Ahlem et al.
2006/0264378	A1	11/2006	Fujii et al.
2006/0264605	A1	11/2006	Fujii
2007/0119969	A1	5/2007	Collins, Jr. et al.
2007/0129760	A1	6/2007	Demarais et al.
2007/0167459	A1	7/2007	Habashita et al.
2008/0233053	A1	9/2008	Gross et al.
2009/0181897	A1	7/2009	Fujii et al.
2010/0143334	A1	6/2010	Peled et al.
2010/0166715	A1	7/2010	Peled et al.
2010/0184694	A1	7/2010	Peled et al.
2010/0222256	A1	9/2010	Fujii
2011/0269686	A1	11/2011	Fujii et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CA	1297007	3/1992
EP	0243153	10/1987

(Continued)

OTHER PUBLICATIONS

Pottgen et al. Int. J. Radiation Oncology Biol. Phys. vol. 76(3). 809-815. 2010.*

(Continued)

Primary Examiner — Amber D Steele

Assistant Examiner — Schuyler Milton

(57) **ABSTRACT**

A method of treating large cell lung cancer in a subject in need thereof is provided. The method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof, thereby treating the large cell lung cancer in the subject.

20 Claims, 8 Drawing Sheets
(8 of 8 Drawing Sheet(s) Filed in Color)

(56) **References Cited**

U.S. PATENT DOCUMENTS

2012/0082687	A1	4/2012	Yeung et al.
2012/0094907	A1	4/2012	Abraham et al.
2012/0207748	A1	8/2012	Peled et al.
2013/0303460	A1	11/2013	Peled
2014/0030211	A1	1/2014	Peled et al.
2016/0082071	A1	3/2016	Peled et al.

FOREIGN PATENT DOCUMENTS

EP	0396158	11/1990
EP	0215126	7/1991
EP	0220520	9/1991
EP	0459516	12/1991
EP	0459795	12/1991
EP	0231819	4/1992
EP	0355811	12/1993
EP	0373679	6/1994
EP	0331186	8/1994
EP	0344796	9/1994
EP	0263490	1/1995
EP	0230980	3/1996
EP	0401384	3/1996
EP	0272703	10/1997
EP	0370205	7/1998
EP	0459630	8/1998
EP	0217404	1/1999
EP	0237545	8/1999
EP	0169566	7/2000
EP	0335423	3/2003
EP	1323730	7/2003
EP	0473268	10/2003
EP	1541585	6/2005
EP	2058395	5/2009
JP	2001-526689	12/2001
JP	2002-506830	3/2002
JP	2002-247843	8/2002
JP	2003-532683	11/2003
WO	WO 91/07988	6/1991
WO	WO 93/15211	8/1993
WO	WO 95/10534	4/1995
WO	WO 98/52598	11/1998
WO	WO 99/47158	9/1999
WO	WO 00/06086	2/2000
WO	WO 00/09152	2/2000
WO	WO 01/38352	5/2001
WO	WO 01/64716	9/2001
WO	WO 01/85196	11/2001
WO	WO 02/20561	3/2002
WO	WO 03/072599	9/2003
WO	WO 2004/020462	3/2004
WO	WO 2004/024178	3/2004
WO	WO 2004/087068	10/2004
WO	WO 2007/022523	2/2007
WO	WO 2007/067280	6/2007
WO	WO 2007/146432	12/2007
WO	WO 2008/017025	2/2008
WO	WO 2008/075369	6/2008
WO	WO 2008/075370	6/2008
WO	WO 2008/075371	6/2008
WO	WO 2010/146578	12/2010
WO	WO 2010/146584	12/2010
WO	WO 2012/095849	7/2012
WO	WO 2013/160895	10/2013
WO	WO 2014/155376	10/2014
WO	WO 2015/019284	2/2015
WO	WO 2015/063768	5/2015

OTHER PUBLICATIONS

Stewart et al. WHO OMS. World Cancer Report. IARC Press. Lyon 2003.*

Burger et al. Expert Rev. Anticancer Ther. 11(4), 621-630 (2011).*

Communication Pursuant to Article 94(3) EPC Dated Mar. 4, 2015 From the European Patent Office Re. Application No. 12702887.6.

Gross et al. "Chemokines in Neuroectodermal Cancers: The Crucial Growth Signal From the Soil", Seminars in Cancer Biology, 19(2): 103-110, Apr. 2009.

Russell et al. "CXCR4 Expression in Neuroblastoma Primary Tumors Is Associated With Clinical Presentation of Bone and Bone Marrow Metastases", Journal of Pediatric Surgery, 39(10): 1506-1511, Oct. 2004.

Zagozdzon et al. "Csk Homologous Kinase Inhibits CXCL12-CXCR4 Signaling in Neuroblastoma", International Journal of Oncology, 32(3): 619-623, Mar. 2008.

European Search Report and the European Search Opinion Dated Oct. 20, 2015 From the European Patent Office Re. Application No. 15169576.4.

International Preliminary Report on Patentability Dated Oct. 8, 2015 From the International Bureau of WIPO Re. Application No. PCT/IL2014/050303.

Abraham et al. "Enhanced Unique Pattern of Hematopoietic Cell Mobilization Induced by the CXCR4 Antagonist 4F-Benzoyl-TN14003", Online Supplement Figure 1, XP055155144, 1 P., May 24, 2007. Fig.1.

Abraham et al. "Enhanced Unique Pattern of Hematopoietic Cell Mobilization Induced by the CXCR4 Antagonist 4F-Benzoyl-TN14003", Stem Cells, 25(9): 2158-2166, Published Online May 24, 2007.

Chen et al. "CXCR4 Inhibition in Tumor Microenvironment Facilitates Anti-Programmed Death Receptor-1 Immunotherapy in Sorafenib-Treated Hepatocellular Carcinoma in Mice", Hepatology, 61: 1591-1602, May 2015.

Topalian et al. "Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer", The New England Journal of Medicine, 366(26): 2443-2454, Jun. 28, 2012.

Office Action Dated Aug. 12, 2015 From the Israel Patent Office Re. Application No. 199468.

Office Action Dated Aug. 13, 2015 From the Israel Patent Office Re. Application No. 199468 and Its Translation Into English.

Office Action Dated Aug. 13, 2015 From the Israel Patent Office Re. Application No. 218405 and Its Translation Into English.

Office Action Dated Sep. 8, 2015 From the Israel Patent Office Re. Application No. 218405.

Advisory Action Before the Filing of an Appeal Brief Dated Aug. 5, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.

Advisory Action Before the Filing of an Appeal Brief Dated Nov. 16, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,699.

Amendment Dated May 15, 2008 After Notice of Allowance of Apr. 14, 2008 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/525,838.

Communication Pursuant to Article 94(3) EPC Dated May 3, 2013 From the European Patent Office Re. Application No. 10176632.7.

Communication Pursuant to Article 94(3) EPC Dated Oct. 4, 2010 From the European Patent Office Re. Application No. 03791288.8.

Communication Pursuant to Article 94(3) EPC Dated Oct. 4, 2013 From the European Patent Office Re. Application No. 07849622.1.

Communication Pursuant to Article 94(3) EPC Dated Oct. 4, 2013 From the European Patent Office Re. Application No. 07849623.9.

Communication Pursuant to Article 94(3) EPC Dated Apr. 9, 2008 From the European Patent Office Re. Application No. 03791288.8.

Communication Pursuant to Article 94(3) EPC Dated Sep. 11, 2013 From the European Patent Office Re. Application No. 10176632.7.

Communication Pursuant to Article 94(3) EPC Dated Dec. 15, 2008 From the European Patent Office Re. Application No. 03791288.8.

Communication Pursuant to Article 94(3) EPC Dated Sep. 15, 2009 From the European Patent Office Re. Application No. 03791288.8.

Communication Pursuant to Article 96(2) EPC Dated Feb. 6, 2006 From the European Patent Office Re. Application No. 10963414.6.

Communication Pursuant to Article 96(2) EPC Dated Mar. 17, 2005 From the European Patent Office Re. Application No. 10963414.6.

Communication Pursuant to Article 96(2) EPC Dated Jul. 18, 2006 From the European Patent Office Re. Application No. 10963414.6.

Communication Pursuant to Article 96(2) EPC Dated Jul. 26, 2007 From the European Patent Office Re. Application No. 10963414.6.

(56) **References Cited**

OTHER PUBLICATIONS

Communication Pursuant to Rule 69 EPC—Reminder Concerning Payment of the Designation Fee (Art. 79(2) EPC) and of the Examination Fee (Art. 94(1) EPC)—and invitation Pursuant to Rule 70a(1) EPC Dated Mar. 12, 2012 From the European Patent Office Re. Application No. 10176632.7.
Completion Requirement Letter Dated Oct. 24, 2013 From the Canadian Intellectual Property Office Re. Application No. 2,765,345.
European Search Report and the European Search Opinion Dated Feb. 3, 2012 From the European Patent Office Re. Application No. 10176632.7.
European Search Report and the European Search Opinion Dated Oct. 21, 2014 From the European Patent Office Re. Application No. 14153703.5.
International Preliminary Report on Patentability Dated Nov. 6, 2014 From the International Bureau of WIPO Re. Application No. PCT/IL2013/050352.
International Preliminary Report on Patentability Dated Jul. 18, 2013 From the International Bureau of WIPO Re. Application No. PCT/IL2012/050008.
International Preliminary Report on Patentability Dated Apr. 19, 2002 From the International Preliminary Examining Authority Re. PCT/JP2001/007668.
International Preliminary Report on Patentability Dated Aug. 19, 2004 From the International Preliminary Examining Authority Re. Application No. PCT/JP2003/010753.
International Preliminary Report on Patentability Dated Jun. 24, 2009 From the International Bureau of WIPO Re. Application No. PCT/IL2007/001596.
International Preliminary Report on Patentability Dated Jun. 24, 2009 From the International Bureau of WIPO Re. Application No. PCT/IL2007/001598.
International Preliminary Report on Patentability Dated Dec. 29, 2011 From the International Bureau of WIPO Re. Application No. PCT/IL2010/000466.
International Search Report and the Written Opinion Dated Sep. 2, 2013 From the International Searching Authority Re. Application No. PCT/IL2013/050352.
International Search Report and the Written Opinion Dated Jun. 4, 2008 From the International Searching Authority Re. Application No. PCT/IL2007/001598.
International Search Report and the Written Opinion Dated Dec. 5, 2008 From the International Searching Authority Re. Application No. PCT/IL2007/001596.
International Search Report and the Written Opinion Dated Oct. 15, 2010 From the International Searching Authority Re. Application No. PCT/IL2010/000466.
International Search Report and the Written Opinion Dated Jun. 24, 2009 From the International Searching Authority Re. Application No. PCT/IL2007/001597.
International Search Report and the Written Opinion Dated May 30, 2012 From the International Searching Authority Re. Application No. PCT/IL2012/050008.
International Search Report Dated Nov. 4, 2003 From the International Searching Authority Re. Application No. PCT/JP2003/010753.
International Search Report Dated Dec. 11, 2001 From the International Searching Authority Re. Application No. PCT/JP2001/007668.
Interview Summary Dated May 3, 2005 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/363,209.
Interview Summary Dated Feb. 21, 2006 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/363,209.
Notice of Reason for Rejection Dated Jul. 8, 2014 From the Japanese Patent Office Re. Application No. 2012-515626 and Its Translation Into English.
Notice of Reason for Rejection Dated Nov. 11, 2014 From the Japanese Patent Office Re. Application No. 2012-515626 and Its Translation Into English.
Notification of Office Action and Search Report Dated Nov. 5, 2013 From the State Intellectual Property Office of the People's Republic of China Re. Application No. 201080035931.5 and Its Translation Into English.
Notification of Office Action and Search Report Dated Mar. 6, 2013 From the State Intellectual Property Office of the People's Republic of China Re. Application No. 201080035931.5 and Its Summary in English.
Notification of the Decision of Rejection Dated Mar. 31, 2014 From the State Intellectual Property Office of the People's Republic of China Re. Application No. 201080035931.5 and Its Translation Into English.
Office Action Dated Apr. 3, 2014 From the Israel Patent Office Re. Application No. 218405 and Its Translation Into English.
Office Action Dated May 4, 2010 From the Israel Patent Office Re. Application No. 199468.
Office Action Dated May 4, 2010 From the Israel Patent Office Re. Application No. 199469.
Office Action Dated Sep. 4, 2011 From the Israel Patent Office Re. Application No. 199468 and Its Translation Into English.
Office Action Dated Apr. 9, 2014 From the Israel Patent Office Re. Application No. 229151 and Its Translation Into English.
Office Action Dated Mar. 13, 2013 From the Israel Patent Office Re. Application No. 199468 and Its Translation Into English.
Office Action Dated May 15, 2014 From the Israel Patent Office Re. Application No. 199468 and Its Translation Into English.
Office Action Dated May 20, 2013 From the Israel Patent Office Re. Application No. 216912 and Its Translation Into English.
Office Action Dated Jul. 28, 2013 From the Israel Patent Office Re. Application No. 199469 and Its Translation Into English.
Office Action Dated Jul. 30, 2014 From the Israel Patent Office Re. Application No. 216912 and Its Translation Into English.
Office Action Dated Oct. 31, 2011 From the Israel Patent Office Re. Application No. 199469 and Its Translation Into English.
Official Action Dated Jul. 1, 2010 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/172,007.
Official Action Dated Nov. 3, 2005 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/363,209.
Official Action Dated May 4, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,699.
Official Action Dated Jul. 5, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,811.
Official Action Dated Mar. 5, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,803.
Official Action Dated Sep. 5, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,699.
Official Action Dated May 6, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/360,751.
Official Action Dated Dec. 7, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,699.
Official Action Dated Dec. 9, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.
Official Action Dated Sep. 10, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/583,746.
Official Action Dated Jul. 11, 2007 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/525,838.
Official Action Dated Sep. 12, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,803.
Official Action Dated May 14, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.
Official Action Dated Jun. 15, 2005 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/363,209.
Official Action Dated Sep. 15, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/889,442.
Official Action Dated Dec. 17, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.
Official Action Dated Jun. 18, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/978,740.
Official Action Dated May 18, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/178,737.
Official Action Dated Apr. 24, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/360,751.

(56) **References Cited**

OTHER PUBLICATIONS

Official Action Dated Jan. 24, 2011 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/172,007.
Official Action Dated Jun. 25, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,811.
Official Action Dated Feb. 27, 2015 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/978,740.
Official Action Dated Aug. 28, 2008 From the US Patent and Trademark Office Re. U.S. Appl. No. 11/497,225.
Official Action Dated Dec. 28, 2011 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/583,746.
Official Action Dated Jan. 29, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/360,751.
Official Action Dated Jan. 31, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,811.
Partial European Search Report Dated Jun. 4, 2014 From the European Patent Office Re. Application No. 14153703.5.
Requisition—Sequence Listing Dated Jan. 5, 2011 From the Canadian Intellectual Property Office Re. Application No. 2,673,719.
Requisition—Sequence Listing Dated May 9, 2013 From the Canadian Intellectual Property Office Re. Application No. 2,673,719.
Requisition by the Examiner Dated Jul. 4, 2013 From the Canadian Intellectual Property Office Re. Application No. 2,537,158.
Requisition by the Examiner Dated Jul. 6, 2012 From the Canadian Intellectual Property Office Re. Application No. 2,421,183.
Requisition by the Examiner Dated Jul. 8, 2013 From the Canadian Intellectual Property Office Re. Application No. 2,421,183.
Requisition by the Examiner Dated Mar. 8, 2011 From the Canadian Intellectual Property Office Re. Application No. 2,421,183.
Requisition by the Examiner Dated Oct. 17, 2011 From the Canadian Intellectual Property Office Re. Application No. 2,537,158.
Requisition by the Examiner Dated Jun. 18, 2013 From the Canadian Intellectual Property Office Re. Application No. 2,673,484.
Requisition by the Examiner Dated May 19, 2011 From the Canadian Intellectual Property Office Re. Application No. 2,421,183.
Requisition by the Examiner Dated Aug. 25, 2009 From the Canadian Intellectual Property Office Re. Application No. 2,421,183.
Requisition by the Examiner Dated May 25, 2010 From the Canadian Intellectual Property Office Re. Application No. 2,537,158.
Requisition by the Examiner on May 26, 2014 From the Canadian Intellectual Property Office Re. Application No. 2,673,484.
Restriction Official Action Dated Mar. 1, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,699.
Restriction Official Action Dated Oct. 3, 2013 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.
Restriction Official Action Dated Feb. 4, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/978,740.
Restriction Official Action Dated Feb. 6, 2007 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/525,838.
Restriction Official Action Dated Apr. 8, 2008 From the US Patent and Trademark Office Re. U.S. Appl. No. 11/497,225.
Restriction Official Action Dated Jul. 9, 2014 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/889,442.
Restriction Official Action Dated Sep. 14, 2011 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/583,746.
Restriction Official Action Dated Feb. 16, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/178,737.
Restriction Official Action Dated Mar. 18, 2005 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/363,209.
Restriction Official Action Dated Mar. 26, 2009 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/172,007.
Restriction Official Action Dated Dec. 28, 2011 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,803.
Restriction Official Action Dated Mar. 28, 2012 From the US Patent and Trademark Office Re. U.S. Appl. No. 12/520,811.
Second Amendment Dated Jul. 14, 2008 to Amendment of May 15, 2008 After Notice of Allowance of Apr. 14, 2008 From the US Patent and Trademark Office Re. U.S. Appl. No. 10/525,838.
Summons to Attend Oral Proceedings Pursuant to Rule 115(1) EPC Dated Dec. 9, 2014 From the European Patent Office Re. Application No. 07849622.1.
Summons to Attend Oral Proceedings Pursuant to Rule 115(1) EPC Dated Feb. 12, 2015 From the European Patent Office Re. Application No. 07849622.1.
Supplementary European Search Report and the European Search Opinion Dated Jan. 3, 2013 From the European Patent Office Re. Application No. 10789103.8.
Supplementary European Search Report and the European Search Opinion Dated Apr. 11, 2011 From the European Patent Office Re. Application No. 07849622.1.
Supplementary European Search Report Dated Nov. 19, 2004 From the European Patent Office Re. Application No. 01963414.6.
Supplementary Partial European Search Report Dated Nov. 28, 2007 From the European Patent Office Re. Application No. 03791288.8.
Translation of Notification of Office Action Dated Mar. 6, 2013 From the State Intellectual Property Office of the People's Republic of China Re. Application No. 201080035931.5.
Translation of Office Action Dated Feb. 1, 2013 From the Japanese Patent Office Re. Application No. 2011-060367.
Translation of Office Action Dated Aug. 11, 2009 From the Japanese Patent Office Re. Application No. 2003-301176.
Translation of Office Action Dated Oct. 19, 2010 From the Japanese Patent Office Re. Application No. 2003-301176.
Translation of Search Report Dated Mar. 6, 2013 From the State Intellectual Property Office of the People's Republic of China Re. Application No. 201080035931.5.
AACR "97th Annual Meeting 2006: Publications", AACR, American Association of Cancer Research, Retreived From the Internet, 2006.
Abraham et al. "Sequential Administration of the High Affinity CXCR4 Antagonist BKT140 Promotes Megakaryopoiesis and Platelet Production", British Journal of Haematology, 163: 248-259, Published Online Aug. 1, 2013.
Arakaki et al. "T134, A Small-Molecule CXCR4 Inhibitor, Has No Cross-Drug Resistance With AMD3100, a CXCR4 Antagonist With a Different Structure", Journal of Virology, XP002199036, 73(2): 1719-1723, Feb. 1999.
Auerbach et al. "Angiogenesis Assays: Problems, Pitfalls and Potential", Cancer and Metastasis Reviews, 19: 167-172, 2000.
Avniel et al. "Involvement of the CXCL12/CXCR4 Pathway in the Recovery of Skin Following Burns", Journal of Investigative Dermatology, 126(2): 468-476, 2006.
Balkwill "The Significance of Cancer Cell Expression of the Chemokine Receptor CXCR4", Seminars in Cancer Biology, 14: 171-179, 2004.
Bork "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle", Genome Research, 10: 398-400, 2000.
Brenner "Errors in Genome Annotation", Trends in Genetics, TIG, 15(4): 132-133, Apr. 1999.
Broxmeyer et al. "Rapid Mobilization of Murine and Human Hematopoietic Stem and Progenitor Cells With AMD3100, a CXCR4 Antagonist", The Journal of Experimental Medicine, XP009076434, 201(8): 1307-1318, Apr. 18, 2005.
Burger et al. "CXCR4 Chemokine Receptor Antagonists: Perspectives in SCLC", Expert Opinion on Investigational Drugs, XP002711650, 18(4): 481-490, Apr. 2009.
Burger et al. "Potential of CXCR4 Antagonists for the Treatment of Metastatic Lung Cancer", Expert Reviews of Anticancer Therapy, XP009152669, 1(4): 621-630, Apr. 1, 2011.
Burger et al. "Small Peptide Inhibitors of the CXCR4 Chemokine Receptor (CD184) Antagonize the Activation, Migration, and Antiapoptotic Responses of CXCL12 in Chronic Lymphocytic Leukemia B Cells", Blood, XP002629047, 106(5): 1824-1830, Sep. 1, 2005.
Carlisle et al. "CXCR4 Expression Heterogeneity in Neuroblastoma Cells Due to Ligand-Independent Regulation", Molecular Cancer, 8(126): 1-14, Dec. 22, 2009.

(56) **References Cited**

OTHER PUBLICATIONS

Coiffier et al. "Chop Chemotherapy Plus Rituximab Compared With Chop Alone in Elderly Patients With Diffuse Large-B-Cell Lymphoma", The New England Journal of Medicine, XP055117777, 346(4): 235-242, Jan. 24, 2002.

Dar et al. "Chemokine Receptor CXCR4-Dependent Internalization and Resecretion of Functional Chemokine SDF-1 by Bone Marrow Endothelial and Stromal Cells", Nature Immunology, 6(10): 1038-1046, Oct. 2005.

Darash-Yahana et al. "Role of High Expression Levels of CXCR4 in Tumor Growth, Vascularization, and Metastatis", The FASEB Journal, 18: 1240-1242, 2004. p. 1242, Last Para.

Di Cesare et al. "In Vitro Characterization and Inhibition of the CXCR4/CXCL12 Chemokine Axis in Human Uveal Melanoma Cell Lines", Cancer Cell International, XP021036445, 7(17): 1-8, Nov. 14, 2007. Abstract, Last Para, Title, p. 5, Right Col., Last Para.

Doerks et al. "Protein Annotation: Detective Work for Function Predicition", Trends in Genetics, 14(6): 248-250, Jun. 1998.

Esler et al. "Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension (The Symplicity HTN-2 Trial): A Randomised Controlled Trial", The Lancet, 376: 1903-1909, Published Online Nov. 17, 2010.

Flomenberg et al. "The Use of AMD3100 Plus G-CSF for Autologous Hematopoietic Progenitor Cell Mobilization Is Superior to G-CSF Alone", Blood, 106(5): 1867-1874, 2005.

Fransen et al. "Suppression of Dualtropic Human Immunodeficiency Virus Type 1 by the CXCR4 Antagonist AMD3100 Is Associated With Efficiency of CXCR4 Use and Baseline Virus Composition", Antimicrobial Agents and Chemotherapy, 52(7): 2608-2615, Apr. 28, 2008.

Fujii et al. "Peptide-Lead CXCR4 Antagonists With High Anti-HIV Activity", Current Opinion in Investigational Drugs, 2(9): 1198-1202, 2001.

Ghobrial et al. "Molecular Mechanisms Involved in Homing and Migration of Plasma Cells in Response to CXCR4", Blood, XP002629051, 104(11): 1-33, Apr. 12, 2005.

Gotoh et al. "Increase of R5 HIV-1 Infection and CCR5 Expression in T Cells Treated With High Concentrations of CXCR4 Antagonists and SDF-1", Journal of Infection and Chemotherapy, 7(1): 28-36, 2001.

Gura "Cancer Models: Systems for Identifying New Drugs Are Often Faulty", Science, 278(5340): 1041-1042, Nov. 7, 1997.

Hatse et al. "CXC-ChemokineReceptor 4 as a Potential New Therapeutic Target for Neuroblastoma and Breast Cancer", International Journal of Cancer, XP001156644, Supplement, 13: 349, Abstract # P 669, Jul. 2002.

Hendrix et al. "Safety, Pharmacokinetics, and Antiviral Activity of AMD3100, a Selective CXCR4 Receptor Inhibitor, in HIV-1 Infection", Journal of Aquired Immune Deficiency Syndromes, JAIDS, 37(2): 1253-1261, Oct. 1, 2004.

Heredia et al. "Rapamycin Causes Down-Regulation of CCR5 and Accumulation of Anti-IIIV Beta-Chemokines: An Approach to Suppress R5 Strains of IIIV-1", Proc. Natl. Acad. Sci. USA, PNAS, 100(18): 10411-10416, Sep. 2, 2003.

Hesselgesser et al. "Neuronal Apoptosis Induced by HIV-1 Gp120 and the Chemokine SDF-1Alpha Is Mediated by the Chemokine Receptor CXCR4", Current Biology, 8: 595-598, Apr. 27, 1998.

Hiramatsu et al. "Synthesis of CXCR4 Antagonists, T140 Derivatives With Improved Biostability, and Their SAR Study", Peptide Science, XP009092185, 203: 213-216, 2002. Abstract, Fig.1.

HIV "Strategic Generation of Anti-AIDS Agents Based on HIV Secondary Receptor Antagonists and Modification of the Agents for Pharmaceutical Use", Report of the Investigation for Development of HIV Medicaments (Year 2000), p. 16-21, 2001. English Translation.

HIV Report of the Investigation for Development of HIV Medicaments (Year 2000), p. 16-21, 2001. Japanese Only!

Jain "Barriers to Drug Delivery in Solid Tumors. Many Tumors Resist Full Penetration by Anticancer Agents. Such Resistance May Help Explain Why Drugs That Eradicate Tumor Cells in Laboratory Dishes Often Fail to Eliminate Malignancies in the Body", Scientific American, p. 58-65, Jul. 1994.

Kaufman et al. "The Effect of Rituximab on Mobilization With AMD3100 Plus G-CSF in Patients With Relapsed or Refractory NHL or HD", Blood, ASH Annual Meeting Abstracts, 110(11/Pt.1): 568A, # 1912, 49th Annual Meeting of the American-Society-of-Hematology, Atlanta, GA, USA, Dec. 8-11, 2007.

Kaufman et al. "The Effect of Rituximab on Mobilization With AMD3100 Plus G-CSF in Patients With Relapsed or Refractory NHL or HD", Database BIOSIS [Online], XP002724332, Database Accession No. PREV200800217184, 4 P., Nov. 16, 2007. Abstract.

Kim et al. "In Vitro Behavior of Hematopoietic Progenitor Cells Under the Influence of Chemoattractants: Stromal Cell-Derived Factor-1, Steel Factor, and the Bone Marrow Environment", Blood, 91(1): 100-110, 1998.

Kollet et al. "Human CD34+CXCR4-Sorted Cells Harbor Intracellular CXCR4, Which Can Be Functionally Expressed and Provide NOD/SCID Repopulation", Blood, 100(8): 2778-2786, 2002.

Koshiba et al. "Expression of Stromal Cell-Derived Factor 1 and CXCR4 Ligand Receptor System in Pancreatic Cancer: A Possible Role for Tumor Progression", Clinical Cancer Research, 6(9): 3530-3535, Sep. 2000.

Kucia et al. "Novel Direct Evidence That Adult Bone Marrow-Derived Very Small Embryonic Like (VSEL) Stem Cells Are Mobilized Into Peripheral Blood—Leukopheresis as a Potential Tool to Isolate Pluripotent Stem Cells for Therapeutic Purposes", Database BIOSIS [Online], Biosciences Information Service, XP002630526, Database Accession No. PREV200800216478, Nov. 2007. & Blood, 110(11/Pt.1): 364A, Nov. 2007 & 49th Annual Meeting of the American Society of Hematology, Atlanta, GA, USA, Dec. 8-11, 2007. Abstract.

Kucia et al. "Trafficking of Normal Stem Cells and Metastasis of Cancer Stem Cells Involve Similar Mechanisms: Pivotal Role of the SDF-1-CXCR4 Axis", Stem Cells, 23(7): 879-894, Aug. 2005.

Lack et al. "A Pharmacokinetic-Pharmacodynamic Model for the Mobilization of CD34+ Hematopoietic Progenitor Cells by AMD3100", Clinical Pharmacology and Therapeutics, 77(5): 427-436, 2005.

Lapidot et al. "How Do Stem Cells Find Their Way Home?", Blood, 106(6): 1901-1910, 2005.

Lapidot et al. "The Essential Roles of the Chemokine SDF-1 and Its Receptor CXCR4 in Human Stem Cell Homing and Repopulation of Transplanted Immune-Deficient NOD/SCID and NOD/SCID/B2m<Null> Mice", Leukemia, 16(10): 1992-2003, 2002.

Levesque et al. "Disruption of the CXCR4/CXCL12 Chemotactic Interaction During Hematopoietic Stem Cell Mobilization Induced by GCSF or Cyclophosphamide", Journal of Clinical Investigation, XP002630527, 111(2): 187-196, Jan. 2003.

Liles et al. "Mobilization of Hematopoietic Progenitor Cells in Healthy Volunteers by AMD3100, a CXCR4 Antagonist", Blood, XP003001859, 102(8): 2728-2730, Oct. 15, 2003.

Martin et al. "Chemokines Acting Via CXCR2 and CXCR4 Control the Release of Neutrophils From the Bone Marrow and Their Return Following Senescence", Immunity, 19(4): 583-593, Oct. 2003.

Matthys et al. "AMD3100, a Potent and Specific Antagonist of the Stromal Cell-Derived Factor-1 Chemokine Receptor CXCR4, Inhibits Autoimmune Joint Inflammation in IFN-Gamma Receptor-Deficient Mice", The Journal of Immunology, 167(8): 4686-4692, 2001.

Menu el al. "The Involvement of Stromal Derived Factor 1Alpha in Homing and Progression of Multiple Myeloma in the 5TMM Model", Haematologica/The Hematology Journal, XP002629046, 91(5): 605-612, May 1, 2006.

Merck "Clinical Aspects of Cancer", The Merck Manual, Jun. 26, 2007.

Merck "Introduction: Overview of Cancer", The Merck Manual, Jun. 26, 2007.

Merck "Rheumatoid Arthritis (RA)", The Merck Manual, 18th Ed., 2005.

Mori et al. "Involvement of Stromal Cell-Derived Factor 1 and CXCR4 Receptor System in Pancreatic Cancer", Gastroenterology, XP009021758, 122(4/Suppl.1): A490, Abstract # T1608, Apr. 2002.

(56) **References Cited**

OTHER PUBLICATIONS

Mueller et al. "Involvement of Chemokine Receptors in Breast Cancer Metastasis", Nature, 410: 50-56, Mar. 2001.

Munk Pedersen et al. "The Chimeric Anti-CD20 Antibody Rituximab Induces Apoptosis in B-Cell Chronic Lymphocytic Leukemia Cells Through a P38 Mitogen Activated Protein-Kinase-Dependent Mechanism", Blood, 99(4): 1314-1319, Feb. 15, 2002.

Nagasawa et al. "Molecular Cloning and Structure of a Pre-B-Cell Growth-Stimulating Factor", Proc. Natl. Acad. sci. USA, 91: 2305-2309, Mar. 1994.

Nakashima et al. "Anti-Human Immunodeficiency Virus Activity of a Novel Synthetic Peptide, T22 ([Tyr-5,12, Lys-7]Polyphemusin II): A Possible Inhibitor of Virus-Cell Fusion", Antimicrobial Agents and Chemotherapy, 36(6): 1249-1255, Jun. 1992.

Neidl "Failure Modes in the Discovery Process", Cancer Drug Design and Discovery, Chap.18.2.2: 427-431, 2008.

Ngo et al. "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox", The Protein Folding Problem and Tertiary Structure Prediction, Chap.14: 433-440, 492-495, 1994.

Omagari et al. "Development of Specific CXCR4 Inhibitors Based on an Anti-IIIV Peptide, T140, and Their Structure-Activity Relationships Study", Peptide Science, 2000(37): 129-132, 2001.

Peled et al. "Dependence of Human Stem Cell Engraftment and Repopulation of NOD/SCID Mice on CXCR4", Science, 283(5403): 845-848, 1999.

Phillips et al. "Epidermal Growth Factor and Hypoxia-Induced Expression of CXC Chemokine Receptor 4 on Non-Small Cell Lung Cancer Cells Is Regulated by the Phosphatidylinositol 3-Kinase/PTEN/AKT/Mammalian Target of Rapamycin Signaling Pathway and Activation of Hypoxia Inducible Factor-1Alpha", The Journal of Biological Chemistry, 280(23): 22473-22481, 2005.

Phillips et al. "The Stromal Derived Factor-1/CXCL12-CXC Chemokine Receptor 4 Biological Axis in Non-Small Cell Lung Cancer Metastasis", 167: 1676-1686, 2003.

Princen et al. "HIV Chemokine Receptor Inhibitors as Novel Anti-HIV Drugs", Cytokine & Growth Factor Reviews, 16(6): 659-677, 2005.

Ratajczak et al. "Stem Cell Plasticity Revisited: CXCR4-Positive Cells Expressing mRNA for Early Muscle, Liver and Neural Cells 'Hide Out' in the Bone Marrow", Leukemia, XP002604057, 18(1): 29-40, Jan. 1, 2004.

Ratajczak et al. "T140 Enhances G-CSF-Induced Mobilization of Hematopoietic Stem Cells", Experimental Hematology, XP009146619, 31(7/Suppl.1): 154, Abstract #280, Jul. 2003. & 32nd Annual Meeting of the International Society for Experimental Hematology, Paris, France, Jul. 5-8, 2003.

Rossi et al. "The Biology of Chemokines and Their Receptors", Annual Reviews of Immunology, 18: 217-242, 2000.

Rubin et al. "A Small-Molecule Antagonist of CXCR4 Inhibits Intracranial Growth of Primary Brain Tumors", Proc. Natl. Acad. Sci. USA, PNAS, 100(23): 13513-13518, Nov. 11, 2003.

Sehn et al. "Treatment of Aggressive Non-Hodgkin's Lymphoma: A North American Perspective", Oncology, XP009177924, 19(4/Suppl.1): Apr. 26-34, 2005.

Shim et al. "Chemokine Receptor CXCR4 as a Therapeutic Target for Neuroectodermal Tumors", Seminars in Cancer Biology, 19: 123-134, 2009.

Skolnick et al. "From Genes to Protein Structure and Function: Novel Applications of Computational Approaches in the Genomic Era", Trends in Biotechnology, TIBTECH, 18(1): 34-39, Jan. 2000.

Sporn et al. "Chemoprevention of Cancer", Carcinogenesis, 21(3): 525-530, 2000.

Su et al. "Differential Expression of CXCR4 Is Associated With the Metastatic Potential of Human Non-Small Cell Lung Cancer Cells", Clinical Cancer Research, XP055076137, 11(23): 8273-8280, Dec. 1, 2005.

Tamamura "Development of Selective Antagonists Against an HIV Second Receptor", Yakugaku Zasshi, 121(11): 781-792, 2001. Abstract in English.

Tamamura et al. "A Future Perspective on the Development of Chemokine Receptor CXCR4 Antagonists", Database EMBASE [Online], XP002675634, Database Accession No. EMB-2008509452, Oct. 2008. & Expert Opinion on Drug Discovery, 3(10): 1155-1166, Oct. 2008.

Tamamura et al. "A Low-Molecular-Weight Inhibitor Against the Chemokine Receptor CXCR4: A Strong Anti-HIV Paptide T140", Biochemical and Biophysical Research Communications, 253(3): 877-882, 1998.

Tamamura et al. "Certification of the Critical Importance of L-3-(2-Naphtyl)Alanine at Position 3 of a Specific CXCR4 Inhibitor, T140, Leads to an Exploratory Performance of Its Downsizing Study", Bioorganic & Medicinal Chemistry, 10: 1417-1426, 2002.

Tamamura et al. "Development of Selective Antagonists Against an IIIV Second Receptor", Yakugaku Zasshi, 121(11): 781-792, 2001. English Translation.

Tamamura et al. "Development of Specific CXCR4 Inhibitors Possessing High Selectivity Indexes as Well as Complete Stability in Serum Based on an Anti-HIV Peptide T140", Bioorganic & Medicinal Chemistry Letters, XP002265743, 11(14): 1897-1902, Jul. 23, 2001. Abstract, Fig.1, p. 1901, r-h Col., Last Sentence Before 'Acknowledgements'.

Tamamura et al. "Downsizing of an HIV-Cell Fusion Inhibitor, T22 ([Tyr5,12, Lys7]-Polyphemusin II), With the Maintenance of Anti-HIV Activity and Solution Structure", Bioorganic & Medicinal Chemistry, 6: 473-479, 1998.

Tamamura el al. "Effective Lowly Cytotoxic Analogs of an HIV-Cell Fusion Inhibitor, T22 ([Tyr5,12, Lys7]-Polyphemusin II)", Bioorganic & Medicinal Chemistry, 6(2): 231-238, 1998.

Tamamura et al. "Efficient Analogs of an Anti-HIV Peptide, T22 ([Tyr5,12, Lys7]-Polyphemusin II), Having Low Cytotoxicity", Peptide Science—Present and Future, Proceedings of the 1st International Peptide Symposium, XP002973954, 1997: 427-429, Jan. 1, 1999. Abstract, Fig.2.

Tamamura et al. "Enhancement of the T140-Based Pharmacophores Leads to the Development of More Potent and Bio-Stable CXCR4 Antagonists", Organic Biomolecular Chemistry, 1: 3663-3669, 2003.

Tamamura et al. "HIV-Cell Fusion Inhibitors Targeted to the HIV Second Receptor: T22 and Its Downsized Analogs With High Activity", Peptide Science, 1998(35): 49-52, 1999.

Tamamura et al. "Pharmacophore Identification of a Specific CXCR4 Inhibitor, T140, Leads to Development of Effective Anti-HIV Agents With Very High Selectivity Indexes", Bioorganic & Medicinal Chemistry Letters, 10(23): 2633-2637, 2000.

Tamamura el al. "T140 Analogs as CXCR4 Antagonists Identified as Anti-Metastatic Agents in the Treatment of Breast Cancer", FEBS Letters, 550(1-3): 79-83, Aug. 28, 2003.

Tamamura et al. "The Therapeutic Potential of CXCR4 Antagonists in the Treatment of IIIV Infection, Cancer Metastasis and Rheumatoid Arthritis", Expert Opinion of Therapeutic Targets, 9(6): 1267-1282, 2005.

Tsutsumi et al. "Therapeutic Potential of the Chemokine Receptor CXCR4 Antagonists as Multifunctional Agents", Peptide Science, XP002629052, 88(2): 279-289, Dec. 13, 2006.

Ulvatne et al. "Short Antibacterial Peptides and Erythromycin Act Synergically Against *Escherichia coli*", Journal of Antimicrobial Chemotherapy, 48: 203-208, 2001.

Voermans et al. "Migratory Behavior of Leukemic Cells From Acute Myeloid Leukemia Patients", Leukemia, 16(4): 650-657, Apr. 2002.

Weekes et al. "Stromal Derived Factor1Alpha Mediates Resistance to mTOR Inhibition by the Preservation of Hypoxia Inducible Factor-1Alpha (HIF-1Alpha) Expression", Proceedings of the Annual Meeting of the American Association for Cancer Research, AACR, 47: 553, Abstract #2341, 2006.

Wells "Additivity of Mutational Effects in Proteins", Biochemistry, 29(37): 8509-8517, Sep. 18, 1990.

Zannettino et al. "Elevated Serum Levels of Stromal-Derived Factor-1Alpha Are Associated With Increased Osteoclast Activity and Osteolytic Bone Disease in Multiple Myeloma Patients", Cancer Research, 65(5): 1700-1709, Mar. 1, 2005. Abstract, p. 1707, Last Para-p. 1708, First Para.

(56) **References Cited**

OTHER PUBLICATIONS

Zhang et al. "Primitive Neuroectodermal Tumors of Adrenal Gland", Japanese Journal of Clinical Oncology, 40(8): 800-804, 2010.

Zhou et al. "CXCR4 Is a Major Chemokine Receptor on Glioma Cells and Mediates Their Survival", The Journal of Biological Chemistry, 277(51): 49481-49487, Dec. 29, 2002.

Zuluaga et al. "Neutropenia Induced in Outbred Mice by a Simplified Low-Dose Cyclophosphamide Regimen: Characterization and Applicability to Diverse Experimental Models of Infectious Diseases", BMC Infectious Diseases, 6(55): 1-10, Mar. 17, 2006.

International Search Report and the Written Opinion Dated Feb. 3, 2015 From the International Searching Authority Re. Application No. PCT/IL2014/050939.

International Search Report and the Written Opinion Dated Jun. 17, 2014 From the International Searching Authority Re. Application No. PCT/IL2014/050303.

Abraham et al. "Enhanced Unique Pattern of Hematopoietic Cell Mobilization Induced by the CXCR4 Antagonist 4F-Benzoyl-TN14003", Stem Cells, 25: 2158-2166, First Published Online May 24, 2007.

Beider et al. "CXR4 Antagonist 4F-Benzoyl-TN14003 Inhibits Leukemia and Multiple Myeloma Tumor Growth", XP028154790, Experimental Hematology, XP028161350, 39(3): 282-292, Nov. 30, 2010. Abstract, p. 282, col. 1, 3, p. 283, col. 2, 4, 6, p. 284, col. 6, 8, p. 286, col. 3, Fig.6.

Jacobi et al. "Impact of CXCR4 Inhibition on FLT3-ITD—Positive Human AML Blasts", Experimental Hematology, XP026913582, 38(3): 180-190, Mar. 1, 2010.

Kumar et al. "Mobilization of Bone Marrow Mesenchymal Stem Cells In Vivo Augments Bone Healing in a Mouse Model of Segmental Bone Defect", Bone, 50(4): 1012-1018, Apr. 2012.

Mandawat et al. "Pan-Histone Deacetylase Inhibitor Panobinostat Depletes CXCR4 Levels and Signaling and Exerts Synergistic Antimyeloid Activity in Combination With CXCR4 Antagonists", Blood, XP002725236, 116(24): 5306-5315, Dec. 9, 2010. p. 5311, col. 4; p. 5312 col. 1.

Peled et al. "Role of CXCR4 in the Pathogenesis of Acute Myeloid Leukemia", Theranostics, XP055164251, 3(1): 34-39, Jan. 13, 2013. Abstract.

Pereg et al. "BL-8040, a CXCR4 Antagonist, Synergizes With the FLT3 Inhibitor AC220 Inducing Apoptosis and Reducing Minimal Residual Disease to Prolong Survival of AML Diseased Mice", Society of Hematologic Oncology, SOHO Annual Meeting Proceedings, XP055164272, 2(1): 203, Sep. 17, 2014. Abstract.

Pitchford et al. "Differential Mobilization of Subsets of Progenitor Cells From the Bone Marrow", Cell Stem Cell, 4: 62-72, Jan. 9, 2009.

Qin et al. "Effect of Cytarabine and Decitabine in Combination in Human Leukemic Cell Lines", Clinical Cancer Research, XP002725241, 13(14): 4225-4232, Jul. 15, 2007. Abstract, Fig. 3a, 4.

Ringe et al. "Towards In Situ Tissue Repair: Human Mesenchymal Stem Cells Express Chemokine Receptors CXCR1, CXCR2 and CCR2, and Migrate Upon Stimulation With CXCL8 But Not CCL2", Journal of Cellular Biochemistry, 101(1): 135-146, May 1, 2007.

Tamamura et al. "Enhancement of the T140-Based Pharmacophores Leads to the Development of More Potent and Bio-Stable CXCR4 Antagonists", Organic Biomolecular Chemistry, 1: 3663-3669, Published in Advance Oct. 1, 2003.

Uy et al. "A Phase 1/2 Study of Chemosensitization With the CXCR4 Antagonist Plerixafor in Replapsed or Refractory Acute Myeloid Leukemia", Blood, XP002725214, 119(17): 3917-3923, Apr. 26, 2012. p. 3917, col. 1-3; p. 3918, col. 3; p. 3919, col. 4; p. 3921, col. 5.

Wynn et al. "A Small Proportion of Mesenchymal Stem Cells Strongly Expresses Functionally Active CXCR4 Receptor Capable of Promoting Migration to Bone Marrow", Blood, 104(9): 2643-2645, Prepublished Online Jul. 13, 2004.

Zeng et al. "Inhibition of CXCR4 With the Novel RCP168 Peptide Overcomes Stroma-Mediated Chemoresistance in Chronic and Acute Leukemias", Molecular Cancer Therapeutics, XP008139367, 5(12): 3113-3121, Dec. 2006. Abstract, p. 3118, r-h Col., Para 2, Fig.6, p. 3120, r-h Col., Para 2.

Zeng et al. "Targeting the Leukemia Microenvironment by CXCR4 Inhibition Overcomes Resistance to Kinase Inhibitors and Chemotherapy in AML", Blood, XP002716127, 113(24): 6215-6224, Jun. 11, 2009. Abstract.

Official Action Dated May 28, 2015 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.

European Search Report and the European Search Opinion Dated Aug. 3, 2015 From the European Patent Office Re. Application No. 15166376.2.

Ghobrial et al. "Molecular Mechanisms Involved in Homing and Migration of Plasma Cells in Response to CXCR4 Stimulation and Downstream Activation of the P13K Pathway", Database BIOSIS [Online], XP002629050, Retrieved From BIOSIS, Database Accession No. PREV200510270159, Nov. 16, 2004. Abstract.

Martin et al. "Tumor Angiogenesis Is Associated With Plasma Levels of Stromal-Derived Factor-1[Alpha] in Patients With Multiple Myeloma", Clinical Cancer Research, XP055204518, 12(23): 6973-6977, Dec. 1, 2006. p. 6973.

Requisition by the Examiner Dated Jun. 25, 2015 From the Canadian Intellectual Property Office Re. Application No. 2,765,345.

Requisition by the Examiner Dated Apr. 15, 2015 From the Canadian Intellectual Property Office Re. Application No. 2,673,719.

Requisition by the Examiner Dated Sep. 22, 2015 From the Canadian Intellectual Property Office Re. Application No. 2,673,484.

Communication Pursuant to Article 94(3) EPC Dated Nov. 6, 2015 From the European Patent Office Re. Application No. 12702887.6.

Office Action Dated Feb. 15, 2016 From the Israel Patent Office Re. Application No. 240924 and Its Translation Into English.

Official Action Dated Jan. 22, 2016 From the US Patent and Trademark Office Re. U.S. Appl. No. 13/378,061.

Notice of Reexamination Dated Mar. 11, 2016 From the Patent Reexamination Board of State Intellectual Property Office of the People's Republic of China Re. Application No. 201080035931.5 and Its Translation Into English.

Restriction Official Action Dated Mar. 22, 2016 From the US Patent and Trademark Office Re. U.S. Appl. No. 14/771,513.

International Preliminary Report on Patentability Dated May 12, 2016 From the International Bureau of WIPO Re. Application No. PCT/IL2014/050939.

Abraham et al. "Enhanced Unique Pattern of Hematopoietic Cell Mobilization Induced by the CXCR4 Antagonist 4F-Benzoyl-TN14003", Stem Cells, XP002629045, 25(9): 2158-2166, May 24, 2007.

Peled et al. "The High-Affinity CXCR4 Antagonist BKT140 Is Safe and Induces a Robust Mobilization of Human CD34+ Cells in Patients With Multiple Myeloma", Clinical Cancer Research, 20(2): 469-479, Published Online Nov. 18, 2013.

* cited by examiner

FIG. 1A

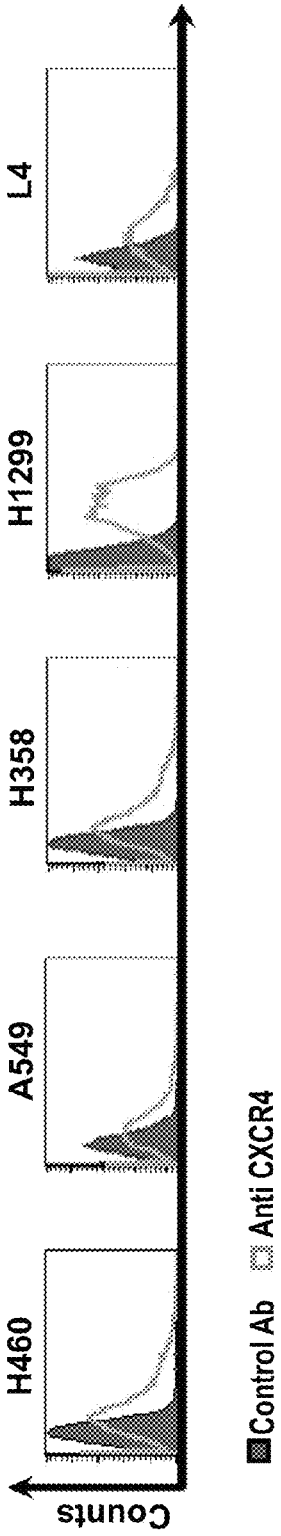


FIG. 1B

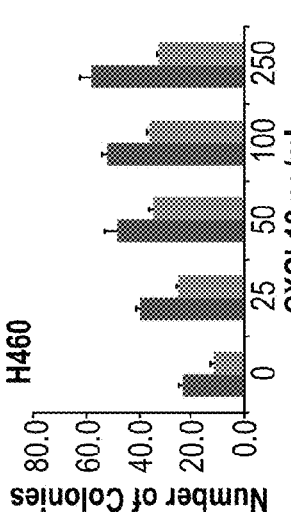


FIG. 1C

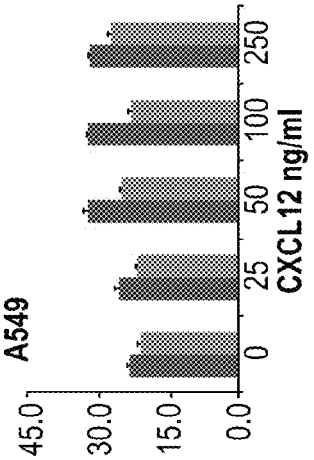


FIG. 1D

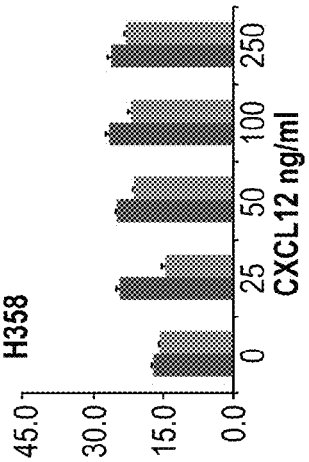


FIG. 1E

FIG. 1F

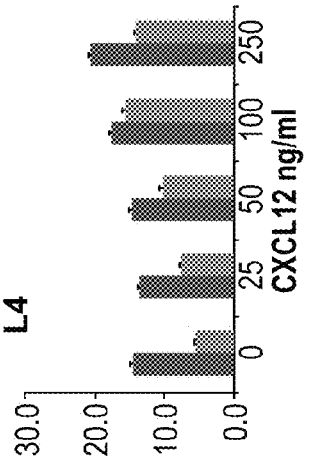


FIG. 2A

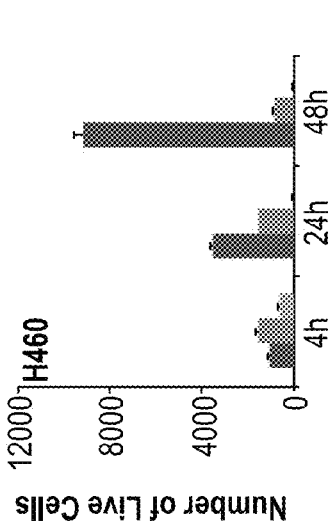


FIG. 2B

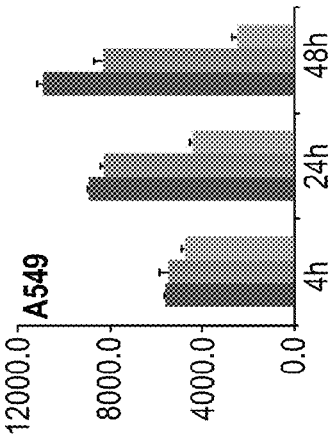


FIG. 2C

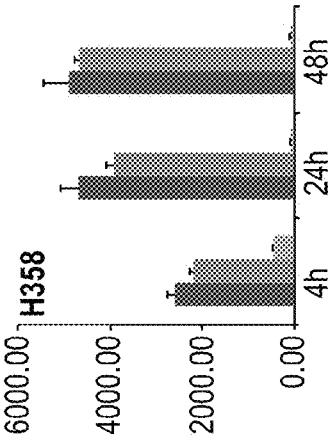


FIG. 2D

FIG. 2E

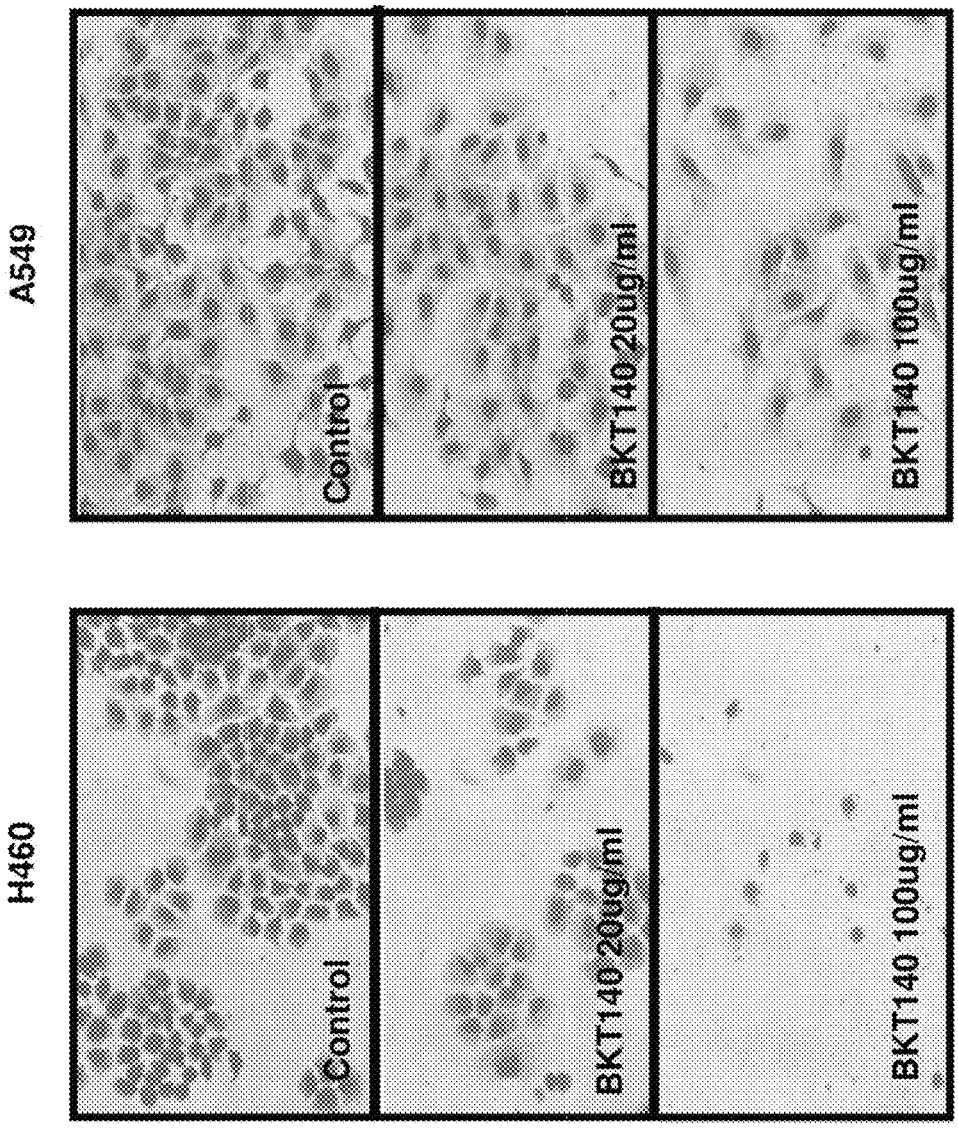


FIG. 2I FIG. 2J FIG. 2K

FIG. 2F FIG. 2G FIG. 2H

FIG. 3C

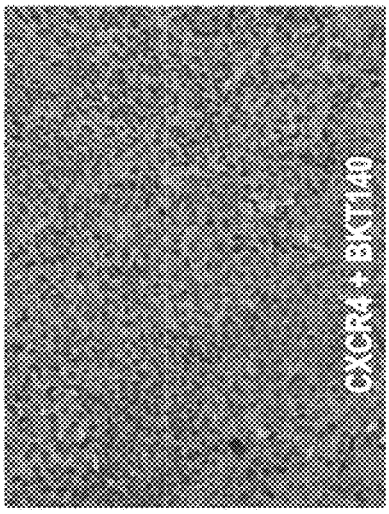


FIG. 3B

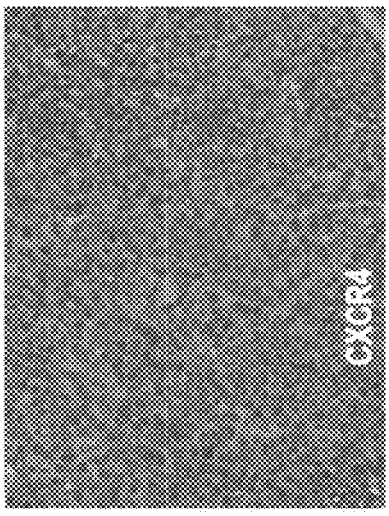


FIG. 3A

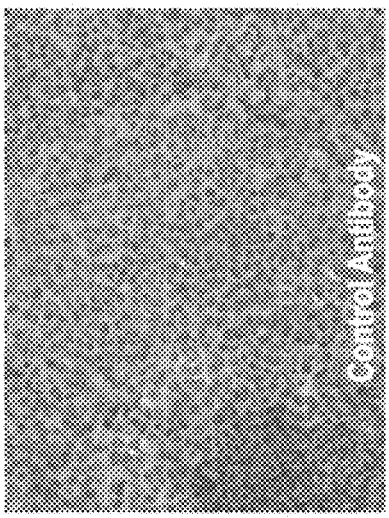


FIG. 3D

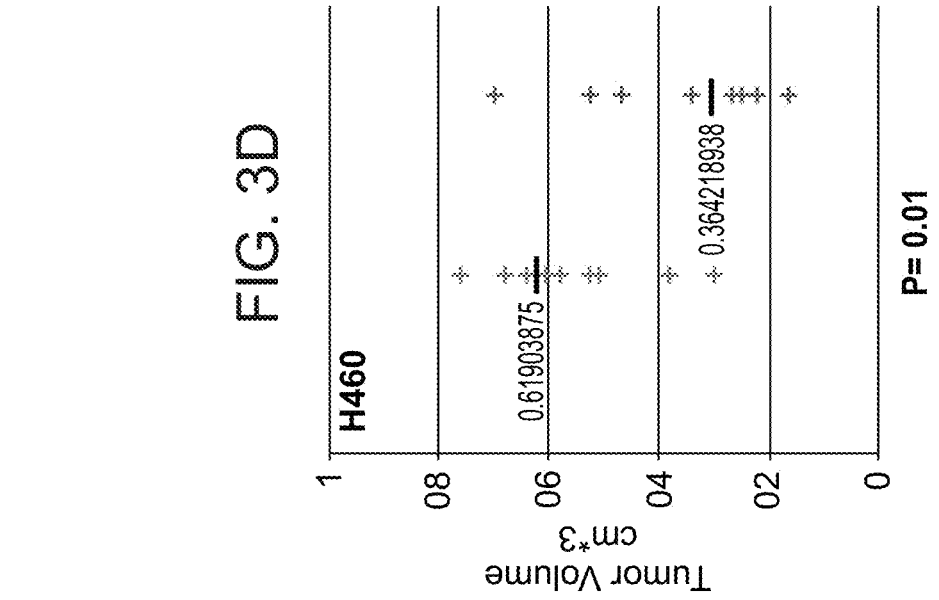
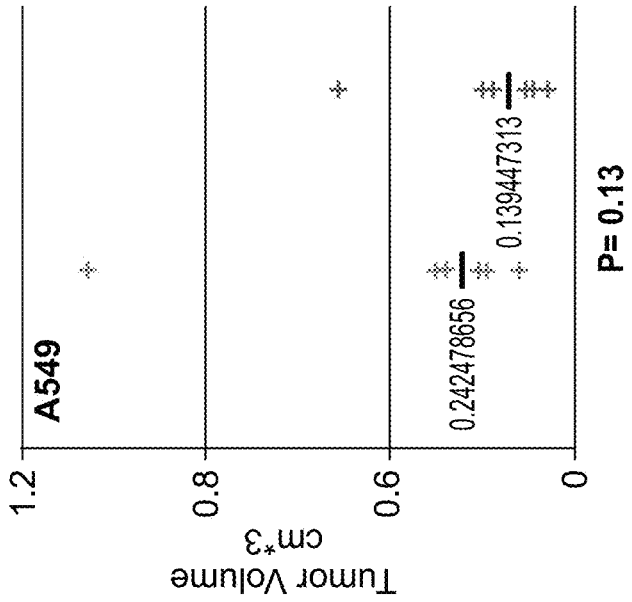

H460
Tumor Volume
cm*3
1
08
06
04
02
0
0.61903875
0.364218938
P= 0.01

FIG. 3E


A549
Tumor Volume
cm*3
1.2
0.8
0.6
0
0.242478656
0.139447313
P= 0.13
CTRL
BKT-140

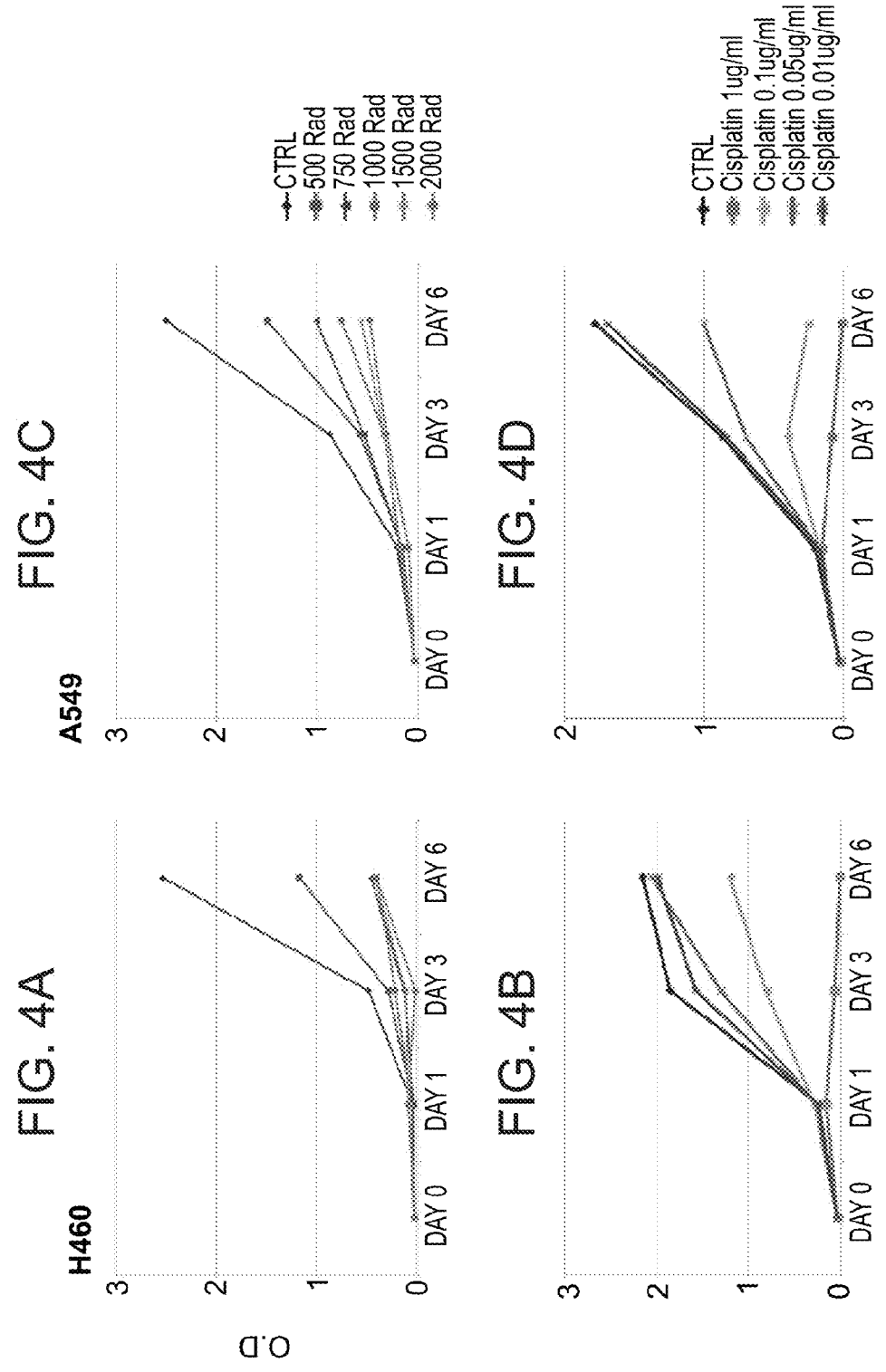


FIG. 4A
H460
O.D
3
2
1
0
DAY 0
DAY 1
DAY 3
DAY 6
FIG. 4B
FIG. 4C
A549
CTRL
500 Rad
750 Rad
1000 Rad
1500 Rad
2000 Rad
FIG. 4D
CTRL
Cisplatin 1ug/ml
Cisplatin 0.1ug/ml
Cisplatin 0.05ug/ml
Cisplatin 0.01ug/ml

FIG. 5A

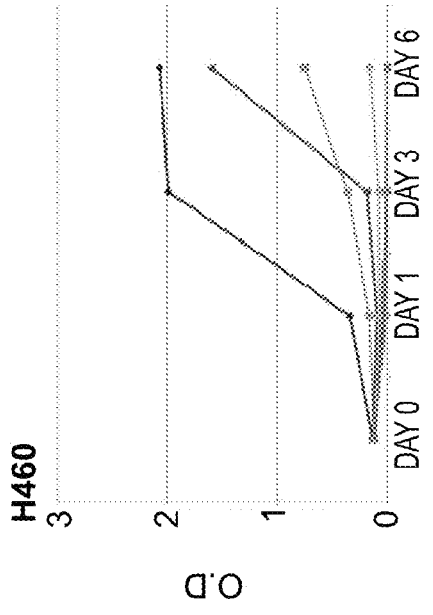


FIG. 5B

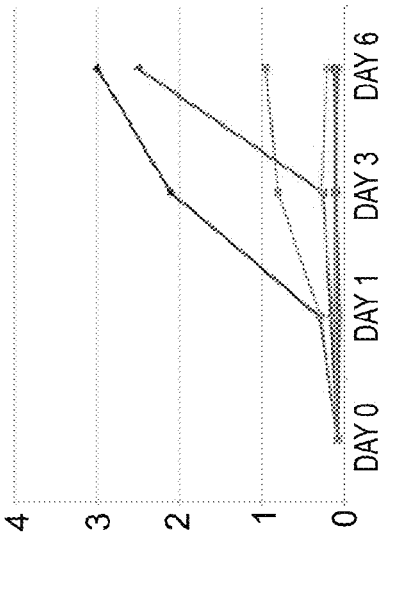


FIG. 5C

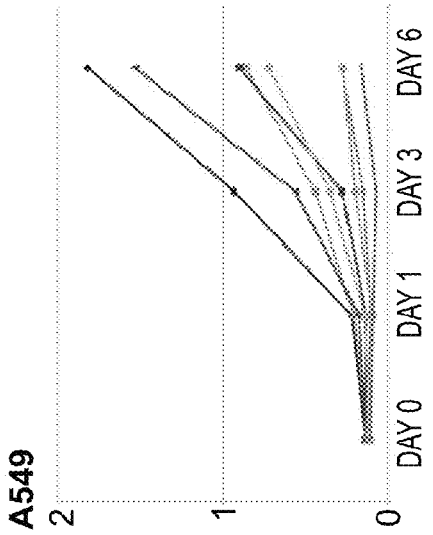
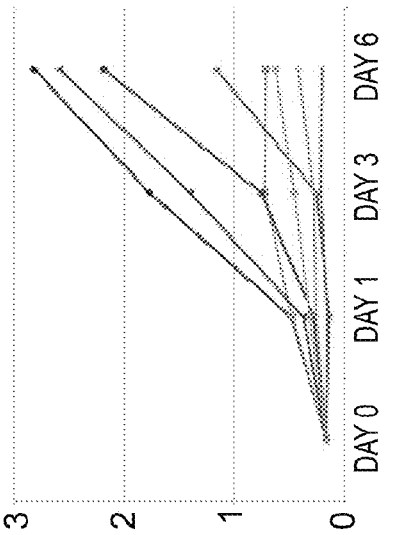


FIG. 5D



PEPTIDES AND USE THEREOF IN THE TREATMENT OF LARGE CELL LUNG CANCER

RELATED APPLICATIONS

This application is a National Phase of PCT Patent Application No. PCT/IL2013/050352 having International filing date of Apr. 24, 2013, which claims the benefit of priority under 35 U.S.C. 517 119(*e*) of U.S. Provisional Patent Application Ser. No. 61/637,334 filed on Apr. 24, 2012. The contents of the above applications are all incorporated by reference as if fully set forth herein in their entirety.

SEQUENCE LISTING STATEMENT

The ASCII file, entitled 60100SequenceListing.txt, created on Aug. 4, 2014, comprising 45,056 bytes, submitted concurrently with the filing of this application is incorporated herein by reference.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to peptides and use thereof in the treatment of large cell lung cancer.

Despite advances in surgery, chemotherapy and radiotherapy over the last decades, the death rate from lung cancer remains a global health problem and worldwide, lung cancer is the most common cause of cancer-related death in men and women. The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), NSCLC being any type of epithelial lung cancer other than small cell lung carcinoma (SCLC). NSCLC accounts for approximately 85% of all lung cancers. NSCLC is typically divided into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma histologies, with approximately 10-15% of all NSCLC being large cell lung cancer. Of the non-small cell lung cancers, large cell lung cancer is usually discovered at a later stage. Furthermore, large cell lung cancers tend to be more aggressive and metastasize. The tumor metastasizes into nearby lymph nodes, into the chest wall and into more distant organs, even when the tumor in the lung is relatively small. As diagnosis occurs at an advanced stage, prognosis is typically poor. Large cell lung cancer is insensitive to chemotherapy compared to small cell lung carcinoma. Thus, treatment of NSCLC typically requires multiple treatments including surgical resection, chemotherapeutic agents and/or radiation therapy used both pre-operatively (neoadjuvant chemotherapy) and post-operatively (adjuvant chemotherapy). Among the most widely used chemotherapeutic drugs are cisplatin and paclitaxel.

The chemokine receptor CXCR4 is a G-protein coupled receptor that is expressed in a wide assortment of normal tissues, and plays a fundamental role in fetal development, mobilization of hematopoietic stem cells and trafficking of naive lymphocytes (Rossi and Zlotnik, 2000). The chemokine CXCL12 (also known as stromal-derived factor-1 or SDF-1) is the only natural ligand of CXCR4. CXCL12 is expressed constitutively in a variety of tissues, including lung, liver, bone marrow and lymph nodes.

Binding of CXCL12 to CXCR4 activates a variety of intracellular signal transduction pathways and effector molecules that regulate cell chemotaxis, adhesion, survival and proliferation. For example, the phosphatidyl-inositol-3-kinase pathway and the mitogen-activated protein (MAP) kinase pathways are regulated by CXCL12 and CXCR4.

Various uses of chemokine receptor modulators, including CXCR4 agonists and antagonists, have been described in the art (Princen et al., 2005; Tamamura et al., 2005; U.S. Pat. No. 7,169,750). The bicyclam drug termed AMD3100, originally discovered as an anti-HIV compound, specifically interacts with CXCR4 in an antagonistic manner. Blocking CXCR4 receptor with AMD3100 results in the mobilization of hematopoietic progenitor cells. Other compounds having CXCR4 regulating activity have been described in the art such as in U.S. Publication No. 2007/0167459, U.S. Pat. No. 6,946,445, and U.S. Patent Application Publication No. 2005/0002939. Moreover, various therapeutic applications have been suggested, such as in cancer therapy. T-140 is a 14-residue synthetic peptide developed as a specific CXCR4 antagonist that suppress HIV-1 (X4-HIV-1) entry to T cells through specific binding to CXCR4 (Tamamura et al., 1998). Subsequently, peptide analogs of T-140 were developed as specific CXCR4 antagonist peptides with inhibitory activity at nanomolar levels (see Tamamura et al., 2003, WO 2002/020561 and WO 2004/020462, WO 2004/087068, WO 00/09152, US 2002/0156034, and WO 2004/024178).

WO 2004/087068 discloses antagonists of chemokine receptors, particularly the CXCR4 receptor, and methods of their use, for example, in the treatment, prevention or diagnosis of cancer. The '068 publication discloses that exemplary CXCR4 peptide antagonists include T140 and derivatives of T140, and that the pathology includes cancer such as breast, brain, pancreatic, ovarian, prostate, kidney, and non-small lung cancer.

WO 00/09152 discloses a variety of therapeutic uses for CXCR4 antagonists such as in the treatment of cancer.

WO 2004/024178 discloses the use of a chemokine receptor antagonist as a ligand for the CXCR4 receptor for the apoptosis-inducing treatment and/or the prevention of the metastatic spread of cancer cells in a patient.

U.S. Publication No. 2002/0156034 discloses the use of CXCR4 antagonists for the treatment of hematopoietic cells such as in cancer.

WO 2002/020561 discloses peptide analogs and derivatives of T-140. The '561 publication demonstrates that the claimed peptides are potent CXCR4 inhibitors, manifesting high anti-HIV virus activity and low cytotoxicity.

WO 2004/020462 discloses additional novel peptide analogs and derivatives of T-140, including 4F-benzoyl-TN14003. The '462 publication further discloses preventive and therapeutic compositions and methods of using same utilizing T-140 analogs for the treatment of cancer, such as lung cancer.

Various therapeutic applications for 4F-benzoyl-TN14003 analogs and derivatives have been recently suggested. Some are described in the following related art.

WO 08/075369 is directed to therapeutic uses of T-140 analog peptides and compositions comprising same. Particularly, the '369 publication provides compositions and methods for providing improved bone marrow transplantation and in the treatment of other conditions wherein bone marrow depletion or suppression is involved.

WO 08/075370 is directed to novel therapeutic uses of T-140 analog peptides, compositions comprising same, and use thereof useful in cancer therapy.

WO 08/075371 is directed to novel therapeutic uses of T-140 analog peptides, compositions comprising same, and use thereof useful for immunomodulation.

WO 10/146578 provides compositions comprising T-140 analog peptides and methods of use thereof, specifically for providing improved platelet levels useful in the treatment and prevention of thrombocytopenia, for controlling bleeding and for inducing or modulating haemostasis.

WO 10/146584 discloses novel polypeptides comprising a chemokine-binding peptide and an Fc fragment. According to the '584 publication the polypeptides are capable of binding to certain chemokines so as to modulate their activity, and are therefore useful in modulating in vivo chemokine-dependent processes such as inflammation, autoimmunity and cancer.

Avniel et al. (Avniel et al., 2006) discloses that blocking the CXCR4/CXCL12 axis by a T-140 analog resulted in a significant reduction in eosinophil accumulation in the dermis and improved epithelialization, thus significantly improving skin recovery after burns.

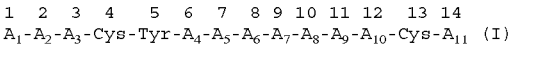
SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a method of treating large cell lung cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof, thereby treating the large cell lung cancer in the subject.

According to an aspect of some embodiments of the present invention there is provided a method of inducing death or inhibiting growth of tumor cells of large cell lung cancer, the method comprising contacting the tumor cells with a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof, thereby inducing death or inhibiting growth of tumor cells of large cell lung cancer.

According to an aspect of some embodiments of the present invention there is provided a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof for use in the treatment of large cell lung cancer.

According to some embodiments of the invention, the analog or derivative comprises an amino acid sequence as set forth in formula (I) or a salt thereof:



wherein:

A_1 is an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue or a N-α-substituted derivative of these amino acids, or A_1 is absent;

A_2 represents an arginine or glutamic acid residue if A_1 is present, or A_2 represents an arginine or glutamic acid residue or a N-a-substituted derivative of these amino acids if A_1 is absent;

A_3 represents an aromatic amino acid residue;

A_4, A_5 and A_9 each independently represents an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue;

A_6 represents a proline, glycine, ornithine, lysine, alanine, citrulline, arginine or glutamic acid residue;

A_7 represents a proline, glycine, ornithine, lysine, alanine, citrulline or arginine residue;

A_8 represents a tyrosine, phenylalanine, alanine, naphthylalanine, citrulline or glutamic acid residue;

A_{10} represents a citrulline, glutamic acid, arginine or lysine residue;

A_{11} represents an arginine, glutamic acid, lysine or citrulline residue wherein the C-terminal carboxyl may be derivatized;

and the cysteine residue of the 4-position or the 13-position can form a disulfide bond, and the amino acids can be of either L or D form.

According to some embodiments of the invention, the peptide is selected from the group consisting of SEQ ID NOS: 1-72.

According to some embodiments of the invention, the peptide is derivatized at the N terminus with a substituted benzoyl group.

According to some embodiments of the invention, the peptide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 36-37 and SEQ ID NO: 53-56.

According to some embodiments of the invention, the peptide consists of SEQ ID NO: 1.

According to some embodiments of the invention, the administering is effected intratumorally.

According to some embodiments of the invention, the method further comprises administering a chemotherapy agent to the subject.

According to some embodiments of the invention, the chemotherapy agent is an alkylating-like agent.

According to some embodiments of the invention, the alkylating-like agent is cisplatin.

According to some embodiments of the invention, the chemotherapy agent is a mitotic inhibitor.

According to some embodiments of the invention, the mitotic inhibitor comprises paclitaxel.

According to some embodiments of the invention, the method further comprises subjecting the subject to radiation therapy.

According to some embodiments of the invention, the peptide induces the tumor cell death.

According to some embodiments of the invention, the peptide inhibits the tumor growth.

According to some embodiments of the invention, the tumor cells comprise tumor stem cells.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. **1**A are graphs illustrating CXCR4 expression in NSCLC cell lines. Representative flow cytometer analyses of CXCR4 staining in H460, A549, H358, H1299 and L4 cells are shown. Control antibody (purple); Anti CXCR4 antibody (green).

FIGS. **1**B-F are bar graphs illustrating colony formation by NSCLC cell lines in the presence of CXCL12 and BKT140 (4F-benzoyl-TN14003, SEQ ID NO: 1). Colony formation by H460 (FIG. **1**B), A549 (FIG. **1**C), H358 (FIG. **1**D), H1299 (FIG. **1**E) and L4 (FIG. **1**F) cells in response to increasing concentrations of CXCL12 (blue) or to increasing concentrations of CXCL12 in combination with 100 μg\ml BKT140 (red) is shown.

FIGS. **2**A-E are bar graphs illustrating proliferation of NSCLC cell lines in the presence of BKT140. The proliferation of H460 (FIG. **2**A), A549 (FIG. **2**B), H358 (FIG. **2**C), H1299 (FIG. **2**D) and L4 (FIG. **2**E) cells in: control medium (blue), in medium supplemented with of 20 μg\ml (red) or in medium supplemented with 100 μg\ml (green) of BKT140 is shown. Indicated time points are 4, 24 and 48 hours post cell seeding.

FIGS. **2**F-K are photographs illustrating representative giemsa staining of H460 (FIGS. **2**F-H) and A549 (FIGS. **2**I-K) cells growing in control medium or in control medium supplemented with 20 μg\ml or 100 μg\ml of BKT140 for 48 hours.

FIGS. **3**A-C are photographs illustrating representative staining of H460 derived xenografts for CXCR4. FIG. **3**A shows staining with control antibody. FIG. **3**B shows staining with anti CXCR4 antibody. FIG. **3**C shows staining with anti CXCR4 antibody of a xenograft that was derived from mice receiving daily BKT140 treatment.

FIGS. **3**D-E are graphs illustrating growth of H460 (FIG. **3**D) and A549 (FIG. **3**E) derived xenografts with or without daily BKT140 treatment. Tumor volume in mice injected with H460 cells (FIG. **3**D) or A549 cells (FIG. **3**E) is shown. Blue crosses indicate control mice (no BKT140 treatment). Red crosses indicate mice that received daily BKT140 injections.

FIGS. **4**A-D are line graphs illustrating proliferation of H460 (FIGS. **4**A-B) and A549 (FIGS. **4**C-D) cells in presence of increasing concentration of cisplatin or increasing doses of radiation. Days 0, 1, 3 and 6 are shown.

FIGS. **5**A-D are line graphs illustrating proliferation of H460 (FIGS. **5**A-B) and A549 (FIGS. **5**C-D) cells in presence of cisplatin 0.1 μg/ml or following irradiation (500 rad) with or without the addition of increasing concentration of BKT140. Days 0, 1, 3 and 6 are shown.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to peptides and uses of same in the treatment of large cell lung cancer.

The principles and operation of the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

CXCR4/CXCL12 interactions promote non-small cell lung cancer (NSCLC) growth and dissemination. In addition, evidence suggests that this axis plays an important role in promoting lung cancer resistance to chemo/radio therapy.

While reducing the present invention to practice, the present inventors have uncovered a novel therapeutic use for the small CXCR4-antagonistic peptide in the treatment of NSCLC.

As is shown hereinbelow and in the Examples section which follows, the present inventors have demonstrated through laborious experimentation the therapeutic efficacy of BKT140 against human NSCLC. Specifically, the present inventors utilized five CXCR4 expressing NSCLC cell lines (see FIG. **1**A), namely, H358, A549, H460, H1299 and L4 and demonstrated that BKT140 has both cytostatic and cytotoxic effects on these cells (see FIGS. **2**A-K). Furthermore, as illustrated in FIGS. **3**A-E, systemic administration of BKT140 significantly delayed the development of H460-derived tumors (i.e. large cell carcinoma) and showed a similar trend for A549-derived tumors (i.e. Adenocarcinoma). Moreover, the present inventors have illustrated that the anti-proliferative effects of BKT140 are additive to those of common chemotherapeutic drugs and radiation treatment (see FIGS. **4**A-D and **5**A-D). Taken together the present teachings portray a therapeutic value to BKT140 in the treatment of non-small cell lung cancers.

Thus, according to an aspect of the invention there is provided a method of treating large cell lung cancer in a subject in need thereof. The method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence as set forth in SEQ ID NO: 1 or an analog or derivative thereof, thereby treating the large cell lung cancer in the subject.

Alternatively or additionally, there is provided a method of inducing death or inhibiting growth of tumor cells of large cell lung cancer. The method comprising contacting (i.e., in-vitro, in-vivo or ex-vivo) the tumor cells with a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof, thereby inducing death or inhibiting growth of tumor cells of large cell lung cancer.

Still alternatively or additionally, there is provided a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof for use in the treatment of large cell lung cancer.

As used herein, the term "peptide" encompasses native peptides (either degradation products, synthetically synthesized peptides or recombinant peptides) and peptidomimetics (typically, synthetically synthesized peptides), as well as peptoids and semipeptoids which are peptide analogs, which may have, for example, modifications rendering the peptides more stable while in a body or more capable of penetrating into cells.

The peptides of the present invention are interchangeably referred to as , 4F-benzoyl-TN14003 (BKT140, SEQ ID NO: 1) analogs and derivatives and are structurally and functionally related to the peptides disclosed in patent applications WO 2002/020561 and WO 2004/020462, also known as "T-140 analogs", as detailed hereinbelow. Without being bound by theory it is suggested that peptides of the invention induce growth arrest and/or death of cancer stem cells of the tumor.

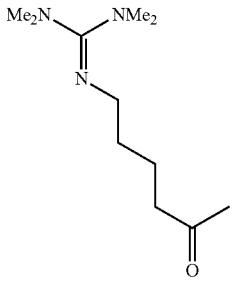
In this specification and drawings, the representations of amino acids, etc. by brevity codes are made by the use of the

codes prescribed by IUPAC-IUB Commission on Biochemical Nomenclature or by the codes customarily used in the relevant art. Examples of such codes are shown below. If an optical isomer exists with respect to an amino acid, it preferably represents the L form unless otherwise expressly specified.

Gly or G: glycine; Ala or A: alanine; Val or V: valine; Leu or L: leucine; Ile or I: isoleucine; Ser or S: serine; Thr or T: threonine; Cys or C: cysteine; Met or M: methionine; Glu or E: glutamic acid; Asp or D: aspartic acid; Lys or K: lysine; Arg or R: arginine; His or H: histidine; Phe or F: phenylalanine; Tyr or Y: tyrosine; Trp or W: tryptophan; Pro or P: proline; Asn or N: asparagine; Gln or Q: glutamine; pGlu: pyroglutamic acid; NaI: 3-(2-naphthyl) alanine; Cit: citrulline; DLys: D-lysine; DCit: D-citrulline; DG1u: D-glutamic acid; Me: methyl group; Et: ethyl group; Bu: butyl group; Ph: phenyl group.

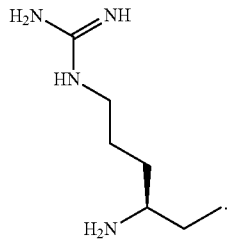
The substituents, protective group and reagents often used in this specification are indicated by the following codes.

BHA: benzhydrylamine
pMBHA: p-methylbenzhydrylamine
Tos: p-toluenesulphonyl
CHO: formyl
HONB: N-hydroxy-5-norbornene-2,3-dicarboximide
OcHex: cyclohexyl ester
Bzl: benzyl
Cl_2-Bzl: dichloro-benzyl
Bom: benzyloxymethyl
Z: benzyloxycarbonyl
Br—Z: 2-bromobenzyloxycarbonyl
Boc: t-butyloxycarbonyl
DCM: dichloromethane
HOBt: 1-hydroxybenzotriazole
DCC: N,N'-dicyclohexylcarbodiimide
TFA: trifluoroacetic acid
DIEA: diisopropylethylamine
Fmoc: N-9-fluorenylmethoxycarbony
DNP: dinitrophenyl
Bum: tertiarybutoxymethyl
Trt: trityl
Ac: acetyl
Guanyl: guanyl
Succinyl: succinyl
glutaryl: glutaryl
TMguanyl: tetramethylguanyl
2F-benzoyl: 2-fluorobenzoyl
4F-benzoyl: 4-fluorobenzoyl
APA: 5 -aminopentanoyl
ACA:6-aminohexanoyl
desamino-Arg: 2-des amino-arginyl
deamino TMG-APA: the following formula (IV):



(IV)

R—CH2: the following formula (V):



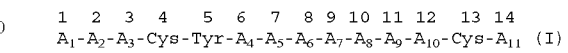
(V)

In N-terminal amino acids, [H—] indicates that the terminal amino group is not derivatized, and in C-terminal amino acids, [—OH] indicates that the terminal carboxyl group is not derivatized.

The 4F-benzoyl-TN14003 analogs of the invention belong to a family of structurally closely related peptides, also known as T-140 analogs. T-140 is a known synthetic peptide having the amino acid sequence H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH (SEQ ID NO: 69, Tamamura et al., 2003, Supra), which was designed based on tachyplesin family polypeptides of the horseshoe crab. The preferable peptides of the invention include analogs and derivatives disclosed in patent applications WO 2002/020561 and WO 2004/020462. These peptides are synthetic peptides of artificial origin.

The term "analog" of SEQ ID NO: 1 as used herein thus relates to a peptide having at least 60% identity to SEQ ID NO: 1, preferably a peptide of Formulae (I) or (II) as defined herein.

In one aspect, the present invention relates to the use of pharmaceutical compositions comprising as an active ingredient a peptide indicated by the following formula (I) or a salt thereof:



wherein:

A_1 in the above-mentioned formula (I) represents an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue (either L or D form) which may be derivatized at the N-terminus, or A_1 is a hydrogen atom, or it is preferable that A_1 is an arginine, citrulline, alanine or D-glutamic acid residue, or A_1 is a hydrogen atom (i.e. the amino acid at this position may be absent).

Examples of "N-terminal derivatized peptides" or "N-α-substituted derivatives" include, but are not limited to, those protected by formyl group; acyl group, e.g., acetyl group, propionyl group, butyryl group, pentanoyl group, C2-6alkanoyl group e.g. hexanoyl group, benzoyl group, arylcarbonyl group e.g. substituted benzoyl group (e.g.:

2-fluorobenzoyl, 3-fluorobenzoyl group, 4-fluorobenzoyl group, 2-bromobenzoyl group, 3-bromobenzoyl group, 4-bromobenzoyl group, 2-nitrobenzoyl group, 3-nitrobenzoyl group, 4-nirtobenzoyl group), succinyl group, glutaryl group; nicotinyl group; isonicotinyl group; alkylsulfonyl group (e.g.: methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, camphorsulfonyl group); arylsulfonyl group (e.g.: p-toluenesulfonyl group, 4-fluorobenzenesufonyl group, mesitylenesulfonyl group, 4-aminobenzenesulfonyl group, dansyl group, 4-bromobenzenesulfonyl group) etc. Or, the N-terminal amino acid group may be absent.

A_2 in the above-mentioned formula (I) represents an arginine or glutamic acid residue (either L or D form) if A1 is an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue (either L or D form) which may be derivatized at the N-terminus, or A_2 represents an arginine or glutamic acid residue (either L or D form) which may be derivatized at the N-terminus if A_1 is absent, or it is preferable that A_2 is an arginine or glutamic acid residue if A_1 is an arginine, citrulline, alanine or glutamic acid residue which may be derivatized at the N-terminus, or A_2 is an arginine or glutamic acid residue which may be derivatized at N-terminus if A_1 is absent. Examples of "peptides derivatized at the N-terminus" include, but are not limited to, the same ones as those mentioned in A1.

A_3 in the above-mentioned formula (I) represents an aromatic amino acid residue (e.g., phenylalanine, tryptophan, 3-(2-naphthyl)alanine, tyrosine, 4-fluorophenylalanine, 3 -(1 -naphthyl)alanine (either L or D form), or preferably, A_3 represents phenylalanine, tryptophan or 3-(2-naphthyl)alanine.

A_4 in the above-mentioned formula (I) represents an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue (either L or D form), or it is preferable that A_4 is an arginine, citrulline, alanine or L- or D-glutamic acid residue.

A_5 in the above-mentioned formula (I) represents an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue (either L or D form), or it is preferable that A_5 is an arginine, citrulline, alanine, lysine or glutamic acid residue.

A_6 in the above-mentioned formula (I) represents a proline, glycine, ornithine, lysine, alanine, citrulline, arginine or glutamic acid residue (either L or D form), or it is preferable that A_6 is a D-lysine, D-alanine, D-citrulline or D-glutamic acid residue.

A_7 in the above-mentioned formula (I) represents a proline, glycine, ornithine, lysine, alanine, citrulline or arginine residue (either L or D form), or it is preferable that A_7 is a proline or alanine residue.

A_8 in the above-mentioned formula (I) represents a tyrosine, phenylalanine, alanine, naphthylalanine, citrulline or glutamic acid residue (either L or D form), or it is preferable that A_8 is a tyrosine, alanine or D-glutamic acid residue.

A_9 in the above-mentioned formula (I) represents an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue (either L or D form), or it is preferable that A_9 is an arginine, citrulline or glutamic acid residue.

A_{10} in the above-mentioned formula (I) represents a citrulline, glutamic acid, arginine or lysine residue (either L or D form), or it is preferable that A_{10} is a citrulline or D-glutamic acid residue.

A_{11} in the above-mentioned formula (I) represents an arginine, glutamic acid, lysine or citrulline residue (either L or D form) which may be derivatized at C-terminus, or it is preferable that A_{11} is an arginine or glutamic acid residue which may be derivatized at the C-terminus

"C-terminal derivatization" or "C-terminal carboxyl derivatization" includes, without limitation, amidation (—$CONH_2$, —CONHR, —CONRR') and esterification (—COOR). Herein, R and R' in amides and esters include, for example, C_{1-6} alkyl group e.g. methyl, ethyl, n-propyl, isopropyl, or n-butyl, C_{3-8} cycloalkyl group e.g. cyclopentyl, cyclohexyl, C_{6-12} aryl group e.g. phenyl and a-naphthyl, phenyl-C_{1-2} alkyl group e.g. benzyl, phenethyl or C_{7-14} aralkyl group e.g. C_{1-2} alkyl group e.g. α-naphthyl methyl group, and additionally, pivaloyloxymethyl group which is generally used as an oral bioavailable ester.

If a peptide of the present invention has carboxy groups (or carboxylates) at side-chain terminals other than C-terminus, the peptide having amidated or esterificated carboxy groups at side-chain terminals is included in the peptides of the present invention. As the amides and esters in this case, for example, the amides and esters exemplified in A_{11} are similarly used. Also, the peptides of the present invention include peptides in which substituents (e.g. —OH, —SH, amino group, imidazole group, indole group, guanidino group, etc.) on the intramolecular amino acid side chains are protected by suitable protective group (e.g. C1-6 acyl group, C2-6 alkanoyl such as formyl group, acetyl group, etc.), or complex peptides such as glycopeptides combined with sugar chain in the above-mentioned peptides.

Salts of the peptides of the present invention include physiologically acceptable salts of acids or bases and particularly, physiologically acceptable acid addition salts are preferable. Such salts are exemplified by salts of inorganic acids (e.g. hydrochloric acid, phosphoric acid, hydrobromic acid, sulfuric acid), or salts of organic acids (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, malic acid, oxalic acid, benzoic acid, methanesulfonic acid, benzenesulfonic acid).

In one embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_1 is a glutamic acid residue or is absent (not present).

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_4 is a glutamic acid residue.

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_6 is a glutamic acid residue.

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_8 is a glutamic acid residue.

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_9 is a glutamic acid residue.

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_5 is an arginine or glutamic acid residue.

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_{10} is a glutamic acid, arginine or lysine residue.

In another embodiment, the composition comprises a peptide as set forth in formula (I) as defined hereinabove, wherein A_{11} is a glutamic acid, lysine or citrulline residue.

In another embodiment, the peptide has an amino acid sequence as set forth in any one of SEQ ID NOS: 1-72 presented in Table 1 herein:

TABLE 1

BKT140 and analogs

Analog	SEQ ID NO:	Amino acid sequence
4F-benzoyl-TN14003	1	4F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2

TABLE 1-continued

BKT140 and analogs

Analog	SEQ ID NO:	Amino acid sequence
AcTC14003	2	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
AcTC14005	3	Ac-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-OH
AcTC14011	4	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-OH
AcTC14013	5	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Cit-Cit-Cys-Arg-OH
AcTC14015	6	Ac-Cit-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
AcTC14017	7	Ac-Cit-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-OH
AcTC14019	8	Ac-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Cit-Cit-Cys-Arg-OH
AcTC14021	9	Ac-Cit-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Cit-Cit-Cys-Arg-OH
AcTC14012	10	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTC14014	11	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Cit-Cit-Cys-Arg-NH_2
AcTC14016	12	Ac-Cit-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTC14018	13	Ac-Cit-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTC14020	14	Ac-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Cit-Cit-Cys-Arg-NH_2
AcTC14022	15	Ac-Cit-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Cit-Cit-Cys-Arg-NH_2
TE14001	16	H-DGlu-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TE14002	17	H-Arg-Glu-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TE14003	18	H-Arg-Arg-Nal-Cys-Tyr-Glu-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TE14004	19	H-Arg-Arg-Nal-Cys-Tyr-Arg-Glu-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TE14005	20	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TE14006	21	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Glu-Cit-Cys-Arg-OH
TE14007	22	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Glu-OH
TE14011	23	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TE14012	24	H-Arg-Arg-Nal-Cys-Tyr-DGlu-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TE14013	25	H-Arg-Arg-Nal-Cys-Tyr-DGlu-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TE14014	26	H-DGlu-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TE14015	27	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-DGlu-Arg-Cit-Cys-Arg-NH_2
TE14016	28	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-DGlu-Cys-Arg-NH_2
AcTE14014	29	Ac-DGlu-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTE14015	30	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-DGlu-Arg-Cit-Cys-Arg-NH_2
AcTE14016	31	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-DGlu-Cys-Arg-NH_2
TF1: AcTE14011	32	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF2: guanyl-TE14011	33	guanyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF3: TMguanyl-TE14011	34	TMguanyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF4: TMguanyl-TE14011 (2-14)	35	TMguanyl-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF5: 4F-benzoyl-TE14011	36	4F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2

TABLE 1-continued

BKT140 and analogs

Analog	SEQ ID NO:	Amino acid sequence
TF6: 2F-benzoyl-TE14011	37	2F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF7: APA-TE14011 (2-14)	38	APA-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF8: desamino-R-TE14011 (2-14)	39	desamino-R-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF9: guanyl-TE14011 (2-14)	40	Guanyl-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF10: succinyl-TE14011 (2-14)	41	succinyl-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF11: glutaryl-TE14011 (2-14)	42	glutaryl-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF12: deaminoTMG-APA-TE14011 (2-14)	43	deaminoTMG-APA-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF15: H-Arg-CH2NH-RTE14011 (2-14)	44	R-CH2-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF17: TE14011 (2-14)	45	H-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF18: TMguanyl-TC14012	46	TMguanyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF19: ACA-TC14012	47	ACA-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TF20: ACA-T140	48	ACA-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TZ14011	49	H-Arg-Arg-Nal-Cys-Tyr-Cit-Arg-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTZ14011	50	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Arg-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTN14003	51	Ac-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
AcTN14005	52	Ac-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
4F-benzoyl-TN14011-Me	53	4F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NHMe
4F-benzoyl-TN14011-Et	54	4F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NHEt
4F-benzoyl-TN14011-iPr	55	4F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-NHiPr
4F-benzoyl-TN14011-tyramine	56	4F-benzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DGlu-Pro-Tyr-Arg-Cit-Cys-Arg-tyramine
TA14001	57	H-Ala-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TA14005	58	H-Arg-Arg-Nal-Cys-Tyr-Ala-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TA14006	59	H-Arg-Arg-Nal-Cys-Tyr-Arg-Ala-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TA14007	60	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DAla-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TA14008	61	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Ala-Tyr-Arg-Cit-Cys-Arg-OH
TA14009	62	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Ala-Arg-Cit-Cys-Arg-OH

TABLE 1-continued

BKT140 and analogs

Analog	SEQ ID NO:	Amino acid sequence
TA14010	63	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Ala-Cit-Cys-Arg-OH
TC14001	64	H-Cit-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TC14003	65	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TN14003	66	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
TC14004	67	H-Arg-Arg-Nal-Cys-Tyr-Arg-Cit-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TC14012	68	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2
T-140	69	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TC14011	70	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TC14005	71	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-OH
TC14018	72	H-Cit-Arg-Nal-Cys-Tyr-Arg-Lys-DCit-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2

In each one of SEQ ID NOS: 1-72, two cysteine residues are preferably coupled in a disulfide bond. Currently preferred peptides according to the present invention are peptides having an amino acid sequence as set forth in any one of SEQ ID NOS: 1-72, wherein each possibility represents a separate embodiment of the present invention.

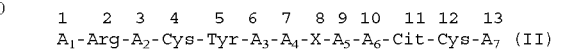
In another particular embodiment, the peptide used in the compositions and methods of the invention consists essentially of an amino acid sequence as set forth in SEQ ID NO: 1. In another preferable embodiment, the peptide used in the compositions and methods of the invention is of an amino acid sequence as set forth in SEQ ID NO:1. In another embodiment, the peptide (analog) is at least 60%, preferably at least 70% and more preferably at least 80% homologous to SEQ ID NO: 1. In another embodiment, the peptide is at least about 90% homologous to SEQ ID NO:1. In another embodiment, the peptide is at least about 95% homologous to SEQ ID NO: 1. Each possibility represents a separate embodiment of the present invention.

It is generally accepted, that the degree of homology between two sequences depends on both the degree of identity in their amino acid sequences and their identity with respect to their length. The peptide homologs of the invention are thus typically about 8-22 amino acids in length, more typically 14-20 amino acid in length or in other embodiments 13-15 amino acids in length, and in particular embodiments about 14 amino acids in length. In various other particular embodiments, the peptide is selected from SEQ ID NOS: 1-72, wherein each possibility represents a separate embodiment of the present invention.

In another particular embodiment, said peptide has an amino acid sequence as set forth in any one of SEQ ID NOS: 1-4, 10, 46, 47, 51-56, 65, 66, 68, 70 and 71. In another particular embodiment, said peptide has an amino acid sequence as set forth in any one of SEQ ID NOS: 4, 10, 46, 47, 68 and 70. In another particular embodiment, said peptide has an amino acid sequence as set forth in any one of SEQ ID NOS: 1, 2, 51, 65 and 66. In another particular embodiment, said peptide has an amino acid sequence as set forth in any one of SEQ ID NOS: 53-56. Each possibility represents a separate embodiment of the invention.

In a preferable particular embodiment, said peptide has an amino acid sequence as set forth in SEQ ID NO: 1. In another particular embodiment, said peptide has an amino acid sequence as set forth in SEQ ID NO:2. In another particular embodiment, said peptide has an amino acid sequence as set forth in SEQ ID NO: 51. In another particular embodiment, said peptide has an amino acid sequence as set forth in SEQ ID NO: 66. Each possibility represents a separate embodiment of the invention.

In another aspect, the invention relates to the use of a pharmaceutical composition comprising a peptide indicated by the following formula (II) or a salt thereof:



wherein:

A_1 represents an arginine, lysine, ornithine, citrulline or alanine residue or an N-α-substituted derivative of these amino acids or a hydrogen atom (namely may be absent);

A_2 represents an aromatic amino acid residue;

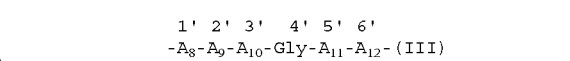
A_3, A_4 and A_6 each independently represent an arginine, lysine, ornithine, citrulline or alanine residue;

A_5 represents a tyrosine, phenylalanine, alanine, naphthylalanine or citrulline residue;

A_7 represents a lysine or arginine residue in which a carboxyl group may be amidated or esterified;

X is selected from the group consisting of:

(i) a peptide residue represented by the following formula (III):



wherein A_8 and A_{12} each independently represents an alanine, valine, leucine, isoleucine, serine, cysteine or methionine residue;

A_9 represents an aromatic amino acid residue, A_{10} is selected from the same amino acid residues as in A_3, A_{11} represents a tyrosine, phenylalanine, tryptophan, alanine, valine, leucine, isoleucine, serine, cysteine or methionine resi-

due, provided that when both of the 1'-position and the 6'-position are cysteine residues, they may be bonded in a disulfide bond,

(ii) a peptide selected from the group consisting of a D-ornithyl-proline, prolyl-D-ornithine, D-lysyl-proline, prolyl-D-lysine, D-arginyl-proline, prolyl-D-arginine, D-citrullyl-proline, D-citrullyl-alanine, D-alanyl-citrulline, prolyl-D-citrulline, glycyl-ornithine, ornithyl-glycine, glycyl-lysine, lysyl-glycine, glycyl-arginine, arginyl-glycine, glycyl-citrulline, citrullyl-glycine, D-alanyl-proline, and D-lysyl-alanine,

and a hydrogen atom of a side chain ω-amino group of D-arginine, L-arginine, D-lysine, L-lysine, D-ornithine or L-ornithine which are constitutional amino acids of said peptide residues may be substituted by a ω-aminoacyl group,

and the peptide residues of (i) and (ii) represent a peptide residue which binds amino acid residues at the 7-position and the 9-position through a peptide bond;

and the cysteine residues at the 4-position and the 12-position may be bonded in a disulfide bond;

provided that, in the above polypeptide or a salt thereof, either of the amino acid residues of A_1, A_3, A_4, A_5, A_6 and A_7 is an alanine or citrulline residue; or

(iii) a peptide residue containing a D-citrulline, D-alanine, citrulline, or alanine residue or a salt thereof.

In the polypeptides of the formula (II) of the present invention, A_1 is preferably an arginine, alanine or citrulline residue; A_2 is preferably a tryptophan or naphthylalanine residue; A_3 is preferably arginine, alanine or citrulline residue; A_4 is preferably a lysine, alanine or citrulline residue; X is preferably a D-lysyl-proline, D-alanyl-proline, D-lysyl-alanine or D-citrullyl-proline residue; A_5 is preferably a tyrosine or alanine residue; A_6 is preferably an arginine, alanine or citrulline residue; A_7 is preferably an arginine residue.

In particular embodiments the peptides of the formula (II) are peptides wherein A_1, A_6 and A_7 are arginine residues, A_2 is a naphthylalanine residue, A_3 is a citrulline residue, A_4 is a lysine residue, X is a D-lysyl-proline residue, and A_5 is a tyrosine residue, a polypeptide of the formula (II) wherein A_1, A_3, A_6 and A_7 are arginine residues, A_2 is a naphthylalanine residue, A_4 is a lysine residue, X is a D-citrullyl-proline residue, and A_5 is a tyrosine residue, a polypeptide of the formula (II) wherein A_1, A_6 and A_7 are arginine residues, A_2 is a naphthylalanine residue, A_3 is a citrulline residue, A_4 is a lysine residue, X is a D-citrullyl-proline residue, A_5 is a tyrosine residue, and a polypeptide of the formula (II) wherein A_1 is a citrulline residue, A_2 is a naphthylalanine residue, A_3, A_6 and A_7 are arginine residues, A_4 is a lysine residue, X is a D-citrullyl-proline residue, A_5 is a tyrosine residue.

The peptides of formula (II) may be exemplified in another embodiment by a peptide of the formula (II) wherein A_1, A_6 and A_7 are arginine residues, A_2 is a naphthylalanine residue, A_3 is a alanine residue, A_4 is a lysine residue, X is a D-lysyl-proline residue, and A_5 is a tyrosine residue, a polypeptide of the formula (II) wherein A_1 is a citrulline residue, A_2 is a naphthylalanine residue, A_3, A_6 and A_7 are arginine residues, A_4 is a lysine residue, X is a D-lysyl-proline residue, and A_5 is a tyrosine residue, a polypeptide of the formula (II) wherein A_1, A_3 and A_7 are arginine residues, A_2 is a naphthylalanine residue, A_4 is a lysine residue, X is a D-lysyl-proline residue, A_5 is a tyrosine residue, and A_6 is a citrulline residue, a polypeptide of the formula (II) wherein A_1 and A_3 are citrulline residues, A_2 is a naphthylalanine residue, A_4 is a lysine residue, X is a D-lysyl-proline residue, A_5 is a tyrosine residue, A_6 and A_7 are arginine residues, and a polypeptide of the formula (II) wherein A_1, A_3 and A_7 are arginine residues, A_2 is a naphthylalanine residue, A_4 is a lysine residue, X is a D-citrullyl-proline residue, A_5 is a tyrosine residue, and A_6 is a citrulline residue.

The amino acid of A_7 as presented in formula II herein is preferably one in which the carboxyl group is amidated for improving stability of the polypeptide in vivo such as in serum, etc.

A peptide of the present invention includes a peptide or its amide, ester or salt containing the amino acid sequence which is substantially the same amino acid to sequence as the sequence of any of the above-mentioned peptides. Here, "substantially the same amino acid sequence" means an amino acid sequence that is qualitatively identical in the activity of the peptide or the biological activity of the peptide (e.g. inhibit large cell lung cancer tumor cells growth and/or induce their death) or the like. Accordingly, quantitative variances are acceptable to some extent (e.g. about 0.01 to 100 times, preferably 0.5 to 20 times, or more preferably 0.5 to 2 times). Therefore, one or more of the amino acids in the amino acid sequences indicated in any of the above-mentioned formula (I), (II) and SEQ ID NOS: 1-72 can have variances, so far as they have any of the above-mentioned properties. That is to say, in the present invention, any peptide (variant peptide) resulting from the variance in the amino acid sequence such as substitution, deletion or insertion (addition) etc. which brings about no significant change (i.e. a qualitatively different change, or a qualitatively identical but quantitatively significantly different change) in the physiological property or chemical property of the original (non-variant) peptide is deemed as substantially the same as the original (non-variant) peptide having no such variance, and, the amino acid sequence of such variant peptide is deemed as substantially the same as the amino acid sequence of the original (non-variant) peptide.

It is a well-known fact that generally, the changes such as substitution, deletion or insertion (addition) of an amino acid in a peptide sequence often do not make a significant change to physiological properties or chemical properties of such peptide. For example, it is generally considered that substitution of a certain amino acid by another amino acid of similar chemical properties results in a peptide having minimized deviation from the properties of the original peptide.

Amino acids are classified, using the similarity of their properties as to one of the criteria, into the following classes, for example: (i) nonpolar (hydrophobic) amino acids (examples: alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, methionine, etc.); (ii) polar (neutral) amino acids (examples: glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, etc.); (iii) basic amino acids carrying positive electric charge (examples: arginine, lysine, histidine, etc.); (iv) acidic amino acids carrying negative electric charge (examples: asparatic acid, glutamic acid, etc.), and accordingly, amino acid substitution within each class can be conservative with regard to the property of a peptide (namely, substitution generating "substantially same" amino acid sequences). In other words, "substantially the same amino acid sequences" may include:

(i) amino acid sequences wherein 1 or more, or, in other embodiments, 1 to 3 amino acids were substituted by other amino acids in the amino acid sequences indicated in the above-mentioned formula (I), (II) and SEQ ID NOS:1-72;

(ii) amino acid sequences wherein 1 or more, or, in other embodiments, 1 to 3 amino acids were deleted in the amino acid sequences indicated in the above-mentioned formula (I), (II) and SEQ ID NOS:1-72;

(iii) amino acid sequences wherein 1 or more or, in other embodiments, 1 to 3 amino acids were added (inserted) in the amino acid sequences indicated in the above-mentioned formula (I), (II) and SEQ ID NOS:1-72; or

(iv) peptides including modifications to amino acids (particularly, the side chains thereof) among the peptides having the amino acid sequences indicated in above (i), (ii) or (iii), or esters, amides or salts thereof.

A peptide of the present invention, if and when the substitution, deletion, insertion (addition), modification, etc. of above (i) to (iv) is intentionally or incidentally provided in the amino acid sequence thereof, can be varied to a stable peptide against heat or protease or a high-activity peptide having more enhanced activity. The peptides of the present invention include also these variant peptides or amides thereof, esters thereof or salts thereof.

Furthermore, among the peptides of the present invention are the peptide consisting of the amino acid sequence indicated in any of the above-mentioned formula (I), (II) and SEQ ID NOS:1-72, and the peptide containing the amino acid sequence sharing the homology of about 50 to 99.9% (preferably, 70 to 99.9%, more preferably 90 to 99.9%) with the foregoing amino acid sequence and having the activities of substantially the same nature as the peptide consisting of the amino acid sequence indicated in any of the above-mentioned formula (I), (II) and SEQ ID NOS:1-72, or amides thereof, esters thereof or salts thereof.

Peptide analogs of the invention include in other embodiments peptides which are identical to SEQ ID NO: 1 or other peptides disclosed herein with respect to their amino acid sequence but have different derivatizing groups (e.g. N' derivatization or C' derivatization), as long as they are qualitatively identical in their anti-tumor activity as the peptides disclosed herein.

The amides, esters or salts of the peptide having the amino acid sequence indicated in any of the above-mentioned SEQ ID NOS: 1-72 include the same ones as are exemplified for the peptide indicated in the above-mentioned formula (I). Preferably, the peptide having the amino acid sequence indicated in any of the above-mentioned SEQ ID NOS: 1-72 is amidated at the carboxyl group of the C-terminal amino acid residue.

The peptides of the present invention including the peptide containing the amino acid sequence indicated in any of the above-mentioned SEQ ID NOS: 1-72 can be produced by conventionally known methods of synthesizing peptides. For the syntheses of peptides, either solid phase peptide synthesis or liquid phase synthesis may be utilized. Namely, an expected peptide can be produced by condensing a partial peptide able to constitute a peptide or an amino acid with remaining portions, and if the product has a protecting group, by eliminating the protecting group. As the known condensation methods and elimination of protecting groups, the following examples (1) to (5) are included:

(1) M. Bodanszky and M. A. Ondetti, Peptide Synthesis, Interscience Publishers, New York (1966).

(2) Schroeder and Luebke, The Peptide, Academic Press, New York (1965).

(3) N. Izumiya, et. al., Peptide Synthesis, Basics and Practice, Maruzen, Tokyo (1975).

(4) H. Yajima and S. Sakakibara, Seikagaku-Jikken-Koza I, Protein Chemistry IV, Tokyo Kagakudojin, Tokyo, pp 205 (1977).

(5) H. Yajima, Zoku-Iyakuhin-no-Kaihatsu, Vol. 14, Peptide Synthesis, Hirokawa Publishing Co., Tokyo (1991).

As practical methods for syntheses of peptides, the following examples can be given:

Generally, commercially available resins for synthesis of polypeptides can be used. Such resins include, for example, chloromethyl resin, hydroxymethyl resin, benzhydroxylamine resin, aminomethyl resin, 4-hydroxybenzylalcohol resin, 4-methylbenzhydroxylamine resin, PAM resin, 4-hydroxymethylmethylphenylacetoamidomethyl resin, polyacrylamide resin, 4-(2',4'-dimetoxyphenyl-hydroxymethyl) phenoxy resin, 4-2',4' -dimetoxyphenyl- Fmoc aminoethylphenoxy resin, etc. Using such resin, an amino acid with suitably protected α-amino group and side chain functional group is condensed on the resin to the sequence of the expected polypeptide in accordance with conventionally known condensation methods. In the last stage of the reaction, the polypeptide is cleared from the resin and simultaneously various protective groups are removed, and then, by carrying out intramolecular disulfide bond-forming reaction in highly diluted solution, the expected polypeptide or amide thereof is obtained. For the above-mentioned condensation of the protected amino acid, various activated reagents usable for the syntheses of polypeptides can be used, but it is particularly better to use carboxyimides. Among such carboxyimides are DCC, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)cabodiimde, etc. For the activation by these, together with racemization inhibitory additives (for example, HOBt, HOOBt), a protected amino acid is added directly to the resin, or after activating the protected amino acid as symmetric acid anhydride or HOBt ester or HOOBt ester, it can be added to ester resin.

Solvents used for the activation of protected amino acids and the condensation with resins can be chosen from among the solvents known to be usable for polypeptide condensation reactions. For example, acid amides such as N,N-dimethylformamide, N,N-dimethylacetoamide and N-methylpyrrolidone, halogenated hydrocarbons such as methylene chloride and chloroform, alcohols such as trifluoroethanol, sulfoxides such as methyl sulfoxide, ethers such as pyridine, dioxane and tetrahydrofuran, nitriles such as acetonitrile and propionitrile, esters such as methyl acetate and ethyl acetate, or appropriated mixtures of the foregoing are used. A solvent used for activation of a protected amino acid or its condensation with resin can be selected from among the solvents known to be usable for condensing reactions of polypeptides. The reaction temperature is appropriately set within the scope known to be applicable to polypeptide bond forming reactions, usually, at −20° C. to 50° C. Activated amino acid derivatives are usually used at 1.5 to 4 times excess. According to the result of tests adopting ninhydrin reaction, if the condensation is insufficient, the repetition of condensation reactions without eliminating protective groups can lead to sufficient condensation. If sufficient condensation is attained by the repetition of reactions, unreacted amino acids can be acetylated by the use of acetic anhydride or acetylimidazole.

The protective group of the amino group used as ingredients include, for example, Z, Boc, tertialypentyloxycarbony, isobornyloxycarbonyl, 4-methoxybenzyloxycabonyl, Cl—Z, Br—Z, adamantyloxycabonyl, trifluoroacetyl, phtaloyl, formyl, 2-nitrophenylsulphenyl, diphenylphosphinothioyl, Fmoc, etc. Carboxyl group can be protected, for example, by alkyl esterification (e.g. straight-chain, branching or circular alkyl esterification of methyl, ethyl, propyl, butyl, tertialbutyl, cyclopentyl, cyclohexyl, cycloheptyl,

cyclooctyl, 2-adamantyl, etc.), aralkyl esterification (e.g. benzylester, 4-nitrobenzylester, 4-methoxybenzylester, 4-chlorbenzylester, benzhydryl esterification), phenacylesterification, benzylcarbonylhydrazidation, tertialybutoxycarbonylhydrazidation, tritylhydrazidation, etc. The hydroxyl group of serine can be protected, for example, by esterification or etherification. The groups suitable for this esterification include, for example, groups derivatized from carboxylic acid such as lower alkanoyl group such as acetyl group, aroyl group such as benzoyl group, benzyloxycarbonyl group, ethoxycarbonyl group. The groups suitable for etherification include, for example, benzyl group, tetrahydropiranyl group, tertiarybutyl group, etc. As the protective groups of phenolic OH group of tyrosine, for example, Bzl, C12-Bzl, 2-nitrobenzyl, Br-Z, tertiarlybutyl, etc. are used. As the protective groups of imidazole of histidine, for example, Tos, 4-methoxy-2,3,6-trimethylbenzenesulfonyl, DNP, benzyloxymethyl, Bum, Boc, Trt, Fmoc etc. are used.

Ingredients with activated carboxyl groups include, for example, corresponding acid anhydride, azide, active ester [ester of alcohol (e.g. pentachlorophenol, 2,4,5-trichlorophenol, 2,4-dinitrophenol, cyanomethylalcohol, p-nitrophenol, HONB, N-hydroxysuccimide, N-hydroxyphtalimide, HOBO] are used. Ingredients with activated amino group include, for example, corresponding phosphoric amide. As the methods to remove (eliminate) protective groups, for example, catalytic reduction in hydrogen airstream in the presence of a catalyst such as Pd-black or Pd-carbon, acid treatment by anhydrous hydrogen fluoride, methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid or a mixture thereof, etc, base treatment by diisopropylethylamine, triethylamine, piperidine, piperadine, etc., and reduction by natrium in liquid ammonia are used. Elimination reaction by the above-mentioned acid treatment is done generally at the temperature of about −20° C. to 40° C., but in the acid treatment, it is effective to add a cation trapping agent such as anisole, phenol, thioanisole, m-cresol, p-cresol, dimethylsulfide, 1,4-butanedithiol, 1,2-ethanedithiol. 2,4-dinitrophenyl group used as the protective group of imidazole of histidine is removed by thiophenol treatment. Formyl group used as the protective group of indole of tryptophan is removed by elimination of protection by the above-mentioned acid treatment in the presence of 1,2-ethanedithiol, 1,4-butanedithiol, etc. and also is removed by alkaline treatment by dilute sodium hydroxide solution, dilute ammonia, etc.

Protection and protective group of functional groups not to be involved in the reaction of ingredients, and elimination of such protective group, and activation of functional groups to be involved in the reaction, etc. can be appropriately selected from among conventionally known groups or conventionally known measures. As alternative methods to obtain amides of polypeptides, there is, for example, a method to manufacture, after amidating and protecting a-carboxyl group of carboxy-terminal amino acid and then extending the peptide chain to the desired chain length on the side of amino group, a polypeptide eliminating the protective group of a-amino group of the N-terminus of such peptide chain and a polypeptide eliminating the protective group of carboxyl group of the C-terminus, and then these two peptides are condensed in the above-mentioned mixed solvent. The details of the condensation reaction are the same as described above. After purifying the protected polypeptide obtained by the condensation, the desired raw polypeptide can be obtained by eliminating all the protective groups by the above-mentioned method. Having purified this raw polypeptide using various known purification methods, if the main fraction is freeze-dried, an amide type of the desired polypeptide can be obtained. To get an ester type of the polypeptide, for example, make an amino acid ester by condensing a-carboxyl group of carboxy-terminal amino acid with the desired alcohols, and then, the ester type of the desired polypeptide can be obtained in the same way as the amide type of the polypeptide.

After the reaction, the peptides of the present invention can be purified and isolated by combining usual purification methods such as solvent extraction, distillation, column chromatography, liquid chromatography, re-crystallization, etc. If a peptide obtained by the above-mentioned methods is a salt-free type, it can be converted to a suitable salt by known methods, or if such peptide is a salt, it can be converted to a salt-free type by known methods.

As mentioned, the peptides of the invention are used for the treating of large cell to lung cancer.

As used herein the phrase "large cell lung cancer" or "large cell carcinomas" are tumors of the lung having large round cells when examined under the microscope, although the tumors themselves tend to be large as well when diagnosed. Large cell carcinomas often occur in the outer regions of the lungs, and tend to grow rapidly and spread more quickly than some other forms of non-small cell lung cancer.

Large cell lung carcinomas constitute only about 10-15% of the non-small cell lung cancers. Large cell carcinomas include all lung cancers that cannot be classified as non small cell lung cancer classified as adenocarcinoma and sequamouns cell carcinoma. The level of CXCR4 expression on the tumor cells can be used to corroborate the type of cancer (see Example 1 of the Examples section, which follows).

As used herein, the term "treating" refers to inhibiting, preventing or arresting the development of a pathology (disease, disorder or condition i.e., large cell lung cancer) and/or causing the reduction, remission, or regression of a pathology. Those of skill in the art will understand that various methodologies and assays can be used to assess the development of a pathology, and similarly, various methodologies and assays may be used to assess the reduction, remission or regression of a pathology.

As used herein, the term "preventing" refers to keeping a disease, disorder or condition from occurring in a subject who may be at risk for the disease, but has not yet been diagnosed as having the disease.

Methods of diagnosing and monitoring large cell lung cancer are well known in the art. Standard methods which are used include, but are not limited to, X-ray or imaging including, but not limited to, PET scan, CT scan. Biopsies of lung tissue can be used to confirm the diagnosis.

As used herein, the term "subject" includes mammals, preferably human beings at any age which suffer from the pathology.

The peptides of some embodiments of the invention can be administered to the subject per se, or in a pharmaceutical composition where it is mixed with suitable carriers or excipients.

As used herein a "pharmaceutical composition" refers to a preparation of one or more of the active ingredients described herein with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

Herein the term "active ingredient" refers to the peptides accountable for the biological effect. Optionally, a plurality

of active ingredient may be included in the formulation such as chemotherapy, radiation agents and the like, as further described hereinbelow.

Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier", which may be used interchangeably, refer to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

Herein, the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Techniques for formulation and administration of drugs may be found in the latest edition of "Remington's Pharmaceutical Sciences", Mack Publishing Co., Easton, Pa., which is herein fully incorporated by reference (Remington: The Science and Practice of Pharmacy, Gennaro, A., Lippincott, Williams & Wilkins, Philadelphia, Pa., 20th ed, 2000).

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

The pharmaceutical compositions of the invention are suitable for administration systemically or in a local manner, for example, via injection of the pharmaceutical composition directly into a tissue region of a patient. In a preferred embodiment, the peptide or the pharmaceutical compositions comprising same is administered locally directly into the tumor i.e., intratumorally.

For injection, the active ingredients of the pharmaceutical composition may be formulated in aqueous solutions (e.g., WFI), preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological salt buffer.

Pharmaceutical compositions for potential administration include aqueous solutions of the active preparation in water-soluble form. Additionally, suspensions of the active ingredients may be prepared as appropriate oily or water-based injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters such as ethyl oleate, triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the active ingredients, to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., a sterile, pyrogen-free, water-based solution, before use.

For oral administration, the pharmaceutical composition can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the pharmaceutical composition to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries as desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, and sodium carbomethyl-cellulose;

and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate, may be added.

Dragee cores are provided with suitable coatings. For this purpose, concentrated to sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active ingredients may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

Alternative embodiments include depots providing sustained release or prolonged duration of activity of the active ingredient in the subject, as are well known in the art.

Pharmaceutical compositions suitable for use in the context of the present invention include compositions wherein the active ingredients are contained in an amount effective to achieve the intended purpose. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any preparation used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from in vitro and cell culture assays. For example, a dose can be formulated in animal models to achieve a desired concentration or titer. Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the active ingredients described herein can be determined by standard pharmaceutical procedures in vitro, in cell cultures or experimental animals (see the Examples section which follows, and Sekido et al. 2002 Cancer Genet Cytogenet 137(1):33-42). The data obtained from these in vitro and cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of adminis-

tration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1).

Exemplary doses of the peptide of the invention for human use may be in some embodiments 0.03-10 mg/kg, 0.1-10 mg/kg, 0.1-2 mg/kg, 0.1-1 mg/kg, 0.3-10 mg/kg, 0.3-2 mg/kg, 0.3-1 mg/kg or 0.3-0.9 mg/kg.

The peptides of the current invention derivatives or analogs thereof can be delivered in a controlled release system. Thus, an implant (e.g., an infusion pump) can be used to administer the peptide such as the one that is used, for example, for delivering insulin or chemotherapy to specific organs or tumors. In one embodiment, the peptide of the invention is administered in combination with a biodegradable, biocompatible polymeric implant, which releases the peptide over a controlled period of time at a selected site. Examples of preferred polymeric materials include, but are not limited to, polyanhydrides, polyorthoesters, polyglycolic acid, polylactic acid, polyethylene vinyl acetate, copolymers and blends thereof (See, Medical applications of controlled release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Fla., the contents of which are hereby incorporated by reference in their entirety). In yet another embodiment, a controlled release system can be placed in proximity to a therapeutic target, thus requiring only a fraction of the systemic dose.

As mentioned hereinabove, in other embodiments, the peptides may be used in combination with anti-cancer treatments, e.g. with one or more chemotherapeutic drugs.

According to an exemplary embodiment, the chemotherapeutic agent is an alkylating-like agent such as Cisplatin, Carboplatin and Nedaplatin.

According to another exemplary embodiment, the chemotherapeutic agent is a mitotic inhibitor such a paclitaxel and docetaxel.

In another embodiment, the compositions and methods of the invention enhance the effectiveness of chemotherapy in a subject afflicted with cancer. Alternatively or additionally, the peptide of the invention is administered along with (or complements) radiation treatment.

Thus, according to a further embodiment of the invention, there is provided an to article of manufacture or a kit comprising a packaging that includes in a first container the peptide of the invention and in another container at least one chemotherapy agent or anti-cancer agent. The article-of-manufacture comprises a label with identification and possibly instructions for the treatment of large cell lung cancer.

In yet another embodiment, the composition or treatment regimen consists of a peptide of the invention as a sole active ingredient.

Compositions of some embodiments of the invention may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accommodated by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a preparation of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition, as is further detailed above.

As used herein the term "about" refers to ±10%.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate the invention in a non limiting fashion.

Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include molecular, biochemical, microbiological and recombinant DNA techniques. Such techniques are thoroughly explained in the literature. See, for example, "Molecular Cloning: A laboratory Manual" Sambrook et al., (1989); "Current Protocols in Molecular Biology" Volumes I-III Ausubel, R. M., ed. (1994); Ausubel et al., "Current Protocols in Molecular Biology", John Wiley and Sons, Baltimore, Maryland (1989); Perbal, "A Practical Guide to Molecular Cloning", John Wiley & Sons, New York (1988); Watson et al., "Recombinant DNA", Scientific American Books, New York; Birren et al. (eds) "Genome Analysis: A Laboratory Manual Series", Vols. 1-4, Cold Spring Harbor Laboratory Press, New York (1998); methodologies as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057; "Cell Biology: A Laboratory Handbook", Volumes I-III Cellis, J. E., ed. (1994); "Current Protocols in Immunology" Volumes I-III Coligan J. E., ed. (1994); Stites et al. (eds), "Basic and Clinical Immunology" (8th Edition), Appleton & Lange, Norwalk, CT (1994); Mishell and Shiigi (eds), "Selected Methods in Cellular Immunology", W. H. Freeman and Co., New York (1980); available immunoassays are extensively described in the patent and scientific literature, see, for example, U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; 4,098,876; 4,879,219; 5,011,771 and 5,281,521; "Oligonucleotide Synthesis" Gait, M. J., ed. (1984); "Nucleic Acid Hybridization" Hames, B. D., and Higgins S. J., eds. (1985); "Transcription and Translation" Hames, B. D., and Higgins S. J., Eds. (1984); "Animal Cell Culture" Freshney, R. I., ed. (1986); "Immobilized Cells and Enzymes" IRL Press, (1986); "A Practical Guide to Molecular Cloning" Perbal, B., (1984) and "Methods in Enzymology" Vol. 1-317, Academic Press; "PCR Protocols: A Guide To Methods And Applications", Academic Press, San Diego, Calif. (1990); Marshak et al., "Strategies for Protein Purification and Characterization—A Laboratory Course Manual" CSHL Press (1996); all of which are incorporated by reference as if fully set forth herein. Other general references are provided throughout this document. The procedures therein are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

Example 1

CXCL12 Induce NSCLC Colony Formation in a CXCR4 Dependant Manner

Materials and Experimental Procedures

Cell Lines

The H460 (large cell carcinoma), A549 (Adenocarcinoma), H358 (Bronchoalveolar carcinoma), H1299 (large cell carcinoma)—cell lines were all purchased from ATCC and were maintained in RPMI (Gibco Laboratories, Grand Island, N.Y.) containing 10% fetal calf serum (FCS), 1 mM L-glutamine, 100 U/ml penicillin, and 0.01 mg/ml streptomycin (Biological Industries, Kibbutz Beth Haemek, Israel). L-4 (a primary NSCLC cell line) was generated from large cell carcinoma as previously described (Wald et al, J Thorac Cardiovasc Surg. 2011 June; 141(6): 1503-12). All cell lines were tested for mycoplasma contamination and were found to be negative.

Flow Cytometry

Logarithmically growing cells were harvested, washed and $1*10^5$ cells were stained with anti-human CXCR4 polyclonal anti-N-terminus antibody (Millipore) for 30 minutes at 4° C. PE-labelled donkey anti rabbit IgG (eBioscience) was used as secondary antibody, incubation time: 30 minutes at 4° C. Cells were then read and analyzed by FACS (Becton Dickinson Immunocytometry Systems), using CellQuest software. Control staining was obtained by adding IgG control or only the secondary antibody to the cells.

Colony Assays

Agar base layer was prepared as follows: 45 ml of RPMI+12% FCS was mixed with 15 ml of RPMI X2+12% FCS and with 15 ml of 2.5% agar in double distilled water. Tumor cells were suspended in RPMI+10% FCS. Cell suspension was mixed in a ratio of 1:3 with the agar base solution. This mixture was then plated on top of a preformed solid agar base. CXCL12, at the concentrations of 25 ng/ml, 50 ng/ml, 100 ng/ml and 250 ng/ml, with or without 100 μg\ml of BKT140, were added to the mixture. Fourteen days later, the number of colonies was counted in ten different fields.

Statistical Analysis

Data was expressed as mean ±standard error (SE) and as absolute values. Continuous data with normal distribution were analyzed using T-test. Categorical data were analyzed using Mann-Whitney U test. A p value of 0.05 was considered significant. * $P<0.05$, ** $P<0.01$. Statistical analyses were performed using (SPSS software, (IBM).

Results

Using flow cytometry, the expression of CXCR4 in five NSCLC cell lines (H358, A549, H460, H1299 and L4) was examined. As shown in FIG. **1**A, all tested cell lines expressed CXCR4. Next, the potential of CXCL12 to induce colony formation in these cell lines was tested. As shown in FIGS. **1**B-F, CXCL12 induced a dose dependant increase in colony formation in all tested NSCLC cell lines. The H460 cell line was most sensitive to CXCL12 stimulation while the A549 cell line was the least sensitive to CXCL12 stimulation. H460 cells showed a 2.5 fold increase in colony number in response to 250 ng/ml CXCL12 while A549 cells showed only a 1.4 fold increase in response to similar CXCL12 concentrations. The addition, on day one of the experiment, of a single dose of BKT140 resulted in reduced colony formation by all tested cell lines. This observation was evident over the entire range of CXCL12 concentrations. The inhibitory effect of BKT140 on colony formation was most evident in H460 and H1299 cell lines and least evident in A549 and H358 cell lines.

Example 2

BKT140 Inhibits NSCLC Proliferation

Materials and Experimental Procedures

Cell Lines

As described in Example 1, above.

Proliferation Assay

To measure cell proliferation, 4000 cells were seeded into 96-well cell culture plates with 200 μl RPMI 1640 medium supplemented with 10% FCS under the following conditions: 37° C., and 5% CO_2. Twenty-four hours later, the medium was to changed to RPMI 1640 supplemented with 1% FCS. 20 μg\ml, 50 μg/ml or 100 μg\ml BKT140, with or without Cisplatin 0.1 μg/ml or paclitaxel 0.1 μg/ml to 1 μg/ml μg/ml were added to the medium. For radiation

experiments, prior to plating of cells, the cells were irradiated at the following doses 500 to 2000 Rad. Cultured cells were fixed with 2.5% Gluteraldehyde at the indicated time points and stained with 1% Methylene Blue. Color extraction was done using 0.1 N HCl. Absorbance of the solution in each well at 570 nm was read with micro-plate reader (Anthos Htll). 6 wells were determined for each time point.

Survival Assay

$1*10^5$ cells\ml were cultured in flat bottom 24-well plates (Corning, N.Y.) with 1000 μl RPMI 1640 medium supplemented with 10% FCS under the following conditions: 37° C., and 5% CO2. 24 hours later, the medium was changed to RPMI 1640 supplemented with either 10% FCS or 1% FCS, with 20 μg\ml or 100 μg\ml BKT140. At indicated time points, cells were harvested, washed and stained with Propidium Iodide solution. The number of live cells was counted and analyzed by flow using FACS (Becton Dickinson Immunocytometry Systems) and CellQuest software.

Giemsa Stain

$1*10^5$ cells\ml were cultured in flat bottom 24-well plates (Corning, N.Y.) with 1000 μl RPMI 1640 medium supplemented with 10% FCS under the following conditions: 37° C., and 5% CO2. 24 hours later, the medium was changed to RPMI 1640 supplemented with 1% FCS with or without 100 μg\ml BKT140. At indicated time points, cells were fixed in 100% methanol for 30 minutes, washed in PBS and stained with 1:20 modified Giemsa stain (Sigma) for twenty minutes. Cells were then rinsed with tap water and images acquired.

Statistical Analysis

As described in Example 1, above.

Results

The potential of BKT140 to inhibit colony formation by NSCLC cell lines prompted to further study its potential anti-proliferative effects. To this end, NSCLC proliferation and survival in the presence or absence of increasing concentration of BKT140 was determined. As shown in FIGS. **2**A-E, BKT140 treatment inhibited to NSCLC proliferation and reduced tumor cell survival in a dose dependant manner. The H460 cell line was most sensitive to BKT140 treatment while the A549 cell line was the least. Treatment with low concentrations of BKT140 (20 μg/ml) was sufficient to completely arrest H460 tumor cell proliferation while treatment with high concentration of BKT140 (100 μg/ml) resulted in tumor cell death. In contrast, treatment with low concentrations of BKT140 (20 μg/ml) did not affect A549 tumor cell proliferation. Nevertheless, treatment with high concentration of BKT140 (100 μg/ml) resulted significantly reduced A549 tumor cell proliferation and also had some cytotoxic effect. The cytostatic and cytotoxic effects of low and high concentrations of BKT140 on H460 and A549 cell lines were also shown in the representative Giemsa stain slides presented in FIGS. **2**F-K.

Example 3

BKT140 Treatment Delays NSCLC Tumor Growth In Vivo

Materials and Experimental Procedures

Cell Lines

As described in Example 1, above.

In Vivo Experiments

$1*10^6$ H460 cells mixed in 100 μl RPMI 1640 and 100 μl matrigel (BD Bioscience) were injected subcutaneously (S.C.) into the right flank of Nude mice. Tumor growth was followed for 19 days. $1*10^6$ A549 cells mixed in 100 μl RPMI 1640 and 100 μl matrigel (BD Bioscience) were injected S.C. into the right flank of Nude mice. Tumor growth was followed for 35 days. Systemic BKT140 administration was performed as follows: BKT140 (400 μg/mice dissolved in PBS) was administered once daily 6/7 days a week, by S.C. injection into the left flank at a point distant at least 1.5 cm from the right sided tumor. Tumors size was calculated by measurement of tumor length and width using the following formula: $4/3*\pi*(\text{length}/2)*(\text{width}/2)\hat{}2$.

Immunohistochemistry

Tissue sections of tumor-bearing Nude mice were routinely fixed with formalin and embedded in paraffin. Antigen retrieval was performed, and sections were stained with either mAb 44708 (R&D Systems, Minneapolis, MN) or 12G5 (R&D Systems) for human CXCR4 (1:100) using a standard indirect avidin-biotin HRP method according to to the manufacturer's instructions. 3-Amino-9-ethylcarbazole was used for color development and sections were counterstained with hematoxylin. As negative controls, sections were stained either with no primary Ab (PBS) or with an isotype-matched control Ab.

Statistical Analysis

As described in Example 1, above.

Results

Once establishing the in vitro anti-proliferative effects of BKT140, these observations where further tested in vivo. The systemic effects and kinetics of S.C. injection of BKT140 were previously described (Abraham M, Beider K, Wald H, Weiss I D, Zipori D, Galun E, et al. The CXCR4 antagonist 4F-benzoyl-TN14003 stimulates the recovery of the bone marrow after transplantation. Leukemia 2009 August; 23(8):1378-88. For example, Abraham et al. reported an increase in mobilization of bone marrow derived cells peaking four to eight hours post S.C. injection of BKT140 and returning to base line at 24 hours post BKT140 injection (Abraham M, Beider K, Wald H, Weiss I D, Zipori D, Galun E, et al. The CXCR4 antagonist 4F-benzoyl-TN14003 stimulates the recovery of the bone marrow after transplantation. Leukemia 2009 August; 23(8):1378-88. The present results showed that BKT140, injected S.C. at a site located distant from the tumor, binds to tumor expressed CXCR4. Tissue sections from H460 derived tumors were tested for CXCR4 expression. Representative staining of tumor tissue with a control antibody and with an anti-CXCR4 antibody are shown in FIGS. **3**A and **3**B, respectively. High expression of CXCR4 by the tumor cells was evident. Tumor tissue section prepared from mice, which were S.C. injected with BKT140 6 hours prior to sacrification of the mice, were also stained for CXCR4. As shown in FIG. **3**C, BKT140 administration completely blocked CXCR4 staining. Next, the effects of daily S.C. injections of BKT140 on NSCLC tumor development were examined. The main focus was on BKT140 most sensitive (H460) and least sensitive (A549) cell lines. BKT140 treatment significantly reduced the volume of H460 derived tumors and showed a much reduced effect for A549 derived tumors (FIGS. **3**D and **3**E). The median tumor volume was decreased by nearly 50% in both cell lines tested (FIGS. **3**D and **3**E).

Example 4

Combining BKT140 with Chemotherapeutic Drugs or Radiation Shows Enhanced Efficacy in Inhibition of NSCLC Proliferation

Materials and Experimental Procedures

Cell Lines

As described in Example 1, above.

Proliferation Assay

As described in Example 2, above.

Statistical Analysis

As described in Example 1, above.

Results

As described in the background section above, currently practiced treatment protocols for advanced NSCLC involve the concomitant or staged administration of chemotherapeutic agents (e.g. cisplatin and paclitaxel) with radiation therapy. The gain of chemo and radio resistance by tumor cells is a key path underlining disease recurrence. Interference with the CXCR4/CXCL12 axis has recently been proposed as a potential path to follow in order to increase tumor sensitivity to chemotherapeutic agents and to radiotherapy. In this regard, the potential of BKT140 to enhance the cytostatic and cytotoxic effects of cisplatin, paclitaxel and radiotherapy on H460 and A549 cell lines was tested. First, proliferation of H460 and A549 cell lines following escalating doses of irradiation (FIGS. **4**A and 4C) and in the presence increasing concentrations of cisplatin (FIGS. **4**B and 4D) and paclitaxel was examined (data not shown). Based on these experiments, for each treatment, a dose/concentration that showed a moderate anti-proliferative effect but did not completely inhibit tumor cell proliferation was defined as follows: for radiation pretreatment, the dose of 500 Rad, for cisplatin the concentration of 0.1 μg/m1 and for paclitaxel the concentration of 0.1 μg /ml. Next, H460 and A549 tumor cell proliferation in the presence of increasing concentration of BKT140 with or without pretreatment with irradiation (FIGS. **5**A and **5**C) or cisplatin (FIGS. **5**B and **5**D) or paclitaxel (data not shown) was tested. Overall an additive anti proliferative effects for BKT140 in conjunction with these treatment protocols was evident (FIG. **5**A-D).

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

REFERENCES

Avniel, S. et al., *J. Invest. Dermatol.* 2006, 126(2): 468-76.

Balkwill, F. *Semi. in Canc. Biol.* 2004, 14: 171-179.

Broxmeyer, H. E. et al., *J. Exp. Med.* 2005, 201(8): 1307-1318.

Dar, A. et al., *Nat. Immunol.* 2005. 6(10): 1038-1046.

Flomenberg, N. et al., *Blood,* 2005, 106(5): 1867-1874.

Kim, C. H. and Broxmeyer H. E., *Blood,* 1998, 91(1): 100-110.

Kollet, O. et al., *Blood,* 2002, 100(8): 2778-2786.

Lack, N. A. et al., *Clin. Pharmacol. Ther.* 2005, 77(5): 427-436.

Lapidot, T. and Kollet, O., *Leukemia,* 2002 16(10): 1992-2003.

Lapidot, T. et al., *Blood,* 2005, 106(6): 1901-1910.

Levesque, J. P. et al., *J. Clin. Invest.* 2003, 111(2): 187-196.

Martin, C. et al., *Immunity,* 2003, 19(4): 583-593.

Muller, A. et al., *Nature,* 2001, 410: 50-56.

Nagasawa, T. et al., *Proc. Nat. Aca. Sci.* 1994, 91: 2305-2309.

Peled, A., et al., *Science,* 1999, 283(5403): 845-848.

Phillips, R. et al., *Amer. J. Respir. Critic. Care Med.* 2003, 167: 1676-1686.

Princen, K. and Schols, D., *Cytokine Grow. Fac. Rev.* 2005, 16(6): 659-677.

Rossi, D. and Zlotnik, A., *Ann. Rev. Immun.* 2000, 18: 217-242.

Tamamura, H. et al., *Biochem. Biophys. Res. Commun.* 1998, 253(3): 877-882.

Tamamura, H. et al., *Org. Biomol. Chem.* 2003, 1: 3663-3669.

Tamamura, H. and Fujii, N., *Expert Opin. Ther. Targets,* 2005, 9(6): 1267-1282.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 72

<210> SEQ ID NO 1
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: 4-fluorobenzoyl conjegated residue
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)

-continued

<223> OTHER INFORMATION: citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: citrulline

<400> SEQUENCE: 1

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 2
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 2

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 3
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 3

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 4
<211> LENGTH: 14
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 4

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 5
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 5

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Xaa Xaa Cys Arg
1 5 10

<210> SEQ ID NO 6
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 6

Xaa Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 7
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 7

Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 8
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 8

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Xaa Xaa Cys Arg
1 5 10

<210> SEQ ID NO 9

-continued

<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 9

Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Xaa Xaa Cys Arg
1 5 10

<210> SEQ ID NO 10
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 10

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 11
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 11

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Xaa Xaa Cys Arg
1 5 10

<210> SEQ ID NO 12
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 12

Xaa Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 13
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature

-continued

<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 13

Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 14
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 14

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Xaa Xaa Cys Arg
1 5 10

<210> SEQ ID NO 15
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 15

-continued

Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Xaa Xaa Cys Arg
1 5 10

<210> SEQ ID NO 16
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 16

Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 17
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 17

Arg Glu Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 18
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature

<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 18

Arg Arg Xaa Cys Tyr Glu Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 19
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 19

Arg Arg Xaa Cys Tyr Arg Glu Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 20
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 20

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 21
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 21

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Glu Xaa Cys Arg
1 5 10

<210> SEQ ID NO 22
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 22

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Glu
1 5 10

<210> SEQ ID NO 23
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 23

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

-continued

<210> SEQ ID NO 24
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 24

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 25
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 25

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 26
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 26

Xaa Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 27
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 27

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Xaa Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 28
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature

-continued

<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: D-Glutamic acid

<400> SEQUENCE: 28

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 29
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 29

Xaa Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 30
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 30

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Xaa Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 31
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: D-Glutamic acid

<400> SEQUENCE: 31

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 32
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature

-continued

<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 32

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 33
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' guanyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 33

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 34
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' tetramethylguanyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)

-continued

<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 34

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 35
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' tetramethylguanyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 35

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 36
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 4-fluorobenzoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 36

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg

-continued

1 5 10

<210> SEQ ID NO 37
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 2-fluorobenzoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 37

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 38
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 5-aminopentanoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 38

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 39
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

-continued

<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 2-desamino-arginyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 39

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 40
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' guanyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 40

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 41
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' succinyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)

-continued

<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 41

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 42
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' glutaryl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 42

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 43
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deamino TMG-APA conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid

-continued

<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 43

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 44
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' R-CH2 conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 44

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 45
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 45

Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

-continued

<210> SEQ ID NO 46
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' tetramethylguanyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 46

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 47
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 6-aminohexanoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 47

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 48
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 6-aminohexanoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 48

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 49
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 49

Arg Arg Xaa Cys Tyr Xaa Arg Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 50
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)

-continued

<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 50

Arg Arg Xaa Cys Tyr Xaa Arg Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 51
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 51

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 52
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' Acetylated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 52

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 53

-continued

<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 4-fluorobenzoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amino ehtyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 53

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 54
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 4-fluorobenzoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amino mehtyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 54

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 55
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 4-fluorobenzoyl conjugated peptide
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amino phenyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 55

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 56
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' 4-fluorobenzoyl conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' tyramine conjugated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Glutamic acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 56

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 57
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature

-continued

<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 57

Ala Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 58
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 58

Arg Arg Xaa Cys Tyr Ala Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 59
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 59

Arg Arg Xaa Cys Tyr Arg Ala Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 60
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:

-continued

<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 60

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 61
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 61

Arg Arg Xaa Cys Tyr Arg Lys Xaa Ala Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 62
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 62

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Ala Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 63
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide

-continued

<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 63

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Ala Xaa Cys Arg
1 5 10

<210> SEQ ID NO 64
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 64

Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 65
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 65

-continued

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 66
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 66

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 67
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 67

Arg Arg Xaa Cys Tyr Arg Xaa Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 68
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature

-continued

<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 68

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 69
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Lysin
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 69

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 70
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)

-continued

<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 70

Arg Arg Xaa Cys Tyr Xaa Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 71
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 71

Arg Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: N' deaminated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: C' amidated peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: 3-(2-naphthyl) alanine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: D-Citrulline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Citrulline

<400> SEQUENCE: 72

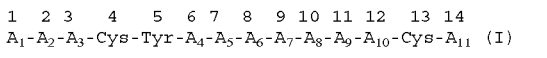
Xaa Arg Xaa Cys Tyr Arg Lys Xaa Pro Tyr Arg Xaa Cys Arg
1 5 10

What is claimed is:

1. A method of treating large cell lung cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof, thereby treating the large cell lung cancer in the subject.

2. A method of inducing death or inhibiting growth of tumor cells of large cell lung cancer, the method comprising contacting the tumor cells with a peptide comprising an amino acid sequence as set forth in SEQ ID NO:1 or an analog or derivative thereof, thereby inducing death or inhibiting growth of tumor cells of large cell lung cancer.

3. The method of claim **1**, wherein the analog or derivative comprises an amino acid sequence as set forth in formula (I) or a salt thereof:



wherein:

A_1 is an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue or a N-α-substituted derivative of these amino acids, or A_1 is absent;

A_2 represents an arginine or glutamic acid residue if A_1 is present, or A_2 represents an arginine or glutamic acid residue or a N-α-substituted derivative of these amino acids if A_1 is absent;

A_3 represents an aromatic amino acid residue;

A_4, A_5 and A_9 each independently represents an arginine, lysine, ornithine, citrulline, alanine or glutamic acid residue;

A_6 represents a proline, glycine, ornithine, lysine, alanine, citrulline, arginine or glutamic acid residue;

A_7 represents a proline, glycine, ornithine, lysine, alanine, citrulline or arginine residue;

A_8 represents a tyrosine, phenylalanine, alanine, naphthylalanine, citrulline or glutamic acid residue;

A_{10} represents a citrulline, glutamic acid, arginine or lysine residue;

A_{11} represents an arginine, glutamic acid, lysine or citrulline residue wherein the C-terminal carboxyl may be derivatized;

and the cysteine residue of the 4-position or the 13-position can form a disulfide bond, and the amino acids can be of either L or D form.

4. The method of claim **1**, wherein the peptide is selected from the group consisting of SEQ ID NOS: 1-72.

5. The method of claim **1**, wherein the peptide is derivatized at the N terminus with a substituted benzoyl group.

6. The method of claim **5**, wherein the peptide is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 36-37 and SEQ ID NO: 53-56.

7. The method of claim **6**, wherein the peptide consists of SEQ ID NO: 1.

8. The method of claim **1**, wherein said administering is effected intratumorally.

9. The method of claim **1**, further comprising administering a chemotherapy agent to the subject.

10. The method of claim **9**, wherein said chemotherapy agent is an alkylating-like agent.

11. The method of claim **10**, wherein said alkylating-like agent is cisplatin.

12. The method of claim **9**, wherein said chemotherapy agent is a mitotic inhibitor.

13. The method of claim **12**, wherein said mitotic inhibitor comprises paclitaxel.

14. The method of claim **1**, further comprising subjecting the subject to radiation therapy.

15. The method of claim **1**, wherein the peptide induces said tumor cell death.

16. The method of claim **1**, wherein the peptide inhibits said tumor growth.

17. The method of claim **2**, wherein the tumor cells comprise tumor stem cells.

18. The method of claim **2**, wherein the peptide is selected from the group consisting of SEQ ID NOS: 1-72.

19. The method of claim **2**, wherein the peptide consists of SEQ ID NO: 1.

20. The method of claim **2**, wherein the peptide induces said tumor cell death.

* * * * *